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TITLE: PET Imaging of Estrogen Metabolism in Breast Cancer

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13. ABSTRACT ***(Maximum 200 Words)***

We propose that estrogen metabolism in breast cancer can be imaged with positron emission tomography (PET). It is well known that many breast tumors associate with estrogen and the presence of catecholestrogens in breast tumors cause changes in the DNA which may lead to uncontrolled cell growth. Catecholestrogens are broken down by an enzyme called catechol-O-methyltransferase (COMT). COMT is known to be elevated in malignant breast tumors, and abnormal COMT genetics have recently been found in individuals with breast cancer. We have developed [^{18}F]Ro41-0960, the first radiotracer for visualizing COMT with PET. The hypothesis that [^{18}F]Ro41-0960 can map COMT was demonstrated both *in vivo* and *ex vivo* in baboon and rodents. We have also adapted our COMT enzyme assay method and performed studies in breast tumor tissue samples from cancer patients undergoing surgery. Preliminary results showed elevated COMT activities in the breast tumor tissues of all patients studied; the difference can be as high as 26 fold increase. We then carried out toxicology tests and submitted an IND application that was finally approved by the FDA on Oct., 1999 to conduct studies in breast cancer patients. After receiving the IND, we have been working on documents that required to get approvals from the HSRRB at US Army Medical Research and local IRBs at BNL and Stony Brook. This novel approach to an extremely important medical problem goes beyond diagnosis in that it seeks to delineate the fundamental biochemical properties and molecular signatures of tumor cells. PET imaging studies on breast cancer patients are underway.

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FOREWORD

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PI - Signature 6/21/01 Date

Table of Contents

INTRODUCTION

The progressive increase in the number of women suffering with breast cancer places a sense of urgency on the development of diagnostic methods. The current method, mammography, is limited by its high degree of false positives which results in unnecessary biopsies. A noninvasive imaging technique to discriminate between benign and malignant breast masses and detect breast cancer metastases to axillary lymph nodes could reduce many breast biopsies and lymph node dissections following mammography prior to the implementation of definitive therapy. We propose to develop a radiotracer to characterize the biochemical profile of breast tumors using positron emission tomography (PET). It has been reported that the activity of catechol-O-methyltransferase (COMT; EC 2.1.1.6), a soluble enzyme that catalyzes the O-methylation of various catechols including catecholestrogens, is elevated in highly malignant human breast tumors (Amin and Ismail, 1983; Assicot, et al., 1977; Hoffman, et al., 1979; Vandewalle, et al.,1985) and abnormal COMT genetics have recently been found in individuals with breast cancer (Lavigne, et al., 1997; Matsui, et al., 2000; Mitrunen, et al. 2001). The feasibility of mapping COMT in vivo with PET is supported by our recent baboon studies using a highly selective and potent fluorine-18 labeled COMT inhibitor, [^{18}F]Ro41-0960 (Ding, et al., 1996; Ding, et al., 1997, 1998). The goals of this proposal are to: (1) correlate the radiotracer bindings with COMT activities in normal and abnormal tissues from the same patient suffering with breast cancer; (2) initiate PET studies in human subjects (female normal controls and females with grade III and IV breast carcinomas). We predict that the uptake of [^{18}F]Ro41-0960 in breast tumor will be substantially greater than background and that the uptake of the radiotracer will be quantitatively different between normal controls and grade III and IV breast carcinomas. It is believed that the localization and quantitation of COMT in breast tumors would be important in understanding its role in the metastases of breast tumor. These studies will set the stage for the development of a diagnostic tool to characterize the biochemical profile of breast tumors in human subjects. If successful, the benefit of this new method would lead to a better understanding of the biochemistry of human breast cancer, reduce the need for unnecessary breast biopsies and enhance the staging capabilities of current diagnostic procedures. Furthermore, this novel approach to an extremely important medical problem goes beyond diagnosis in that it seeks to delineate the fundamental biochemical properties and molecular signatures of tumor cells.

Technical Objectives

Specific Aim 1.
In vitro studies in breast tumor tissue samples from cancer patients undergoing surgery: We will determine whether the degree of binding of [^{18}F]Ro41-0960 is sensitive to and reflects the activity of COMT. The correlation between the radiotracer bindings and COMT activities will serve as a model prior to human PET studies.

Specific Aim 2.
Human PET imaging: We will determine feasibility of PET imaging of COMT with [^{18}F]Ro 41-0960 in human breast cancer patients with palpable breast carcinomas. As part of these studies, we will correlate [^{18}F]Ro41-0960 binding with COMT levels obtained by analysis of biopsied tissue. For this specific aim, in order to conduct PET scanning in human breast cancer patients, we have to: (a) carry out toxicology studies and obtain an IND for using [^{18}F]Ro41-0960 in humans; (b) obtain approvals for carrying out studies in human from both the Human Subjects Research Review Board (HSRRB) at the US Army Medical Research and Material Command, and from local IRBs, including our institute (BNL) and collaborating institute (SUNY at Stony Brook). Breast cancer patients will be recruited from Stony Brook Hospital, and PET scans with [^{18}F]Ro41-0960 will be conducted on patients at BNL.

PROGRESS REPORT

Specific Aim (1): Correlate [^{18}F]Ro41-0960 binding with COMT activities in normal and abnormal tissues from the same patient suffering with breast cancer.

We have demonstrated in baboon and mouse that the binding of [^{18}F]Ro41-0960 to COMT sites in periphery is saturable and sensitive to COMT inhibition [Ding, et al.,1996; Ding, et al.,1998; Ding, et al.,1997]. An *ex vivo* approach in which we correlated the radiotracer uptake with COMT activities in rodents further demonstrated the ability of [^{18}F]Ro41-0960 in mapping COMT activity *in vivo* [Ding, et al.,1999]. We have also adapted our COMT enzyme assay method and performed studies in breast tumor tissue samples from cancer patients undergoing surgery. COMT activities in normal and abnormal human breast tissues from the same patient were compared. This will serve as a model prior to human studies.

COMT activities in normal and abnormal human breast tissues from the same patient were compared. Protein assay was used to normalize the amount of protein used in each experiment, and COMT activity was expressed as pmole of radioactive metanephrine formed per 20 min per mg of cytosol protein [Lowry, et al., 1951]. Though COMT activities varied among subjects, preliminary results showed elevated COMT activities in the breast tumor tissues of all patients studied; the difference can be as high as a 26 fold increase. This could be a potential signal to noise ratio for the future PET studies with [^{18}F]Ro41-0960 in breast cancer patients. The most important finding is that these data were consistent with the pathology reports obtained for each patient.

Specific Aim (2): Initiate studies in human subjects (females with positive needle biopsy and palpable breast tumor). This specific aim has three major goals: (a) carry out toxicology studies and obtain an IND for using [^{18}F]Ro41-0960 in humans; (b) obtain

approvals for carrying out studies in human from both the Human Subjects Research Review Board (HSRRB) at the US Army Medical Research and Material Command, and from local IRBs, including our institute (BNL) and collaborating institute (SUNY at Stony Brook); (c) PET scanning in human breast cancer patients.

(a) carry out toxicology studies and obtain an IND for using [^{18}F]Ro41-0960 in humans:

On February 1998, we submitted an IND to apply for permission to carry out human PET studies with [^{18}F]Ro41-0960 and have been in communication with the FDA since then. Though the amount of [^{18}F]Ro41-0960 which we will use in humans is very small (a total dose of 5 μg required for a PET study is on the order of $1x10^6$ below its lethal dose), the FDA requires a toxicology study be performed by a GLP laboratory before they can approve the use of the tracer in PET studies. We purchased an actute toxicity study from Covance Laboratory (Princeton, NJ) in the rat. The acute toxicity of Ro41-0960 was evaluated in female rats when the test material was administered as a single intravenous injection. All animals appeared normal throughout the study. There were no significant differences in body weights or body weight gains between the control and test groups. Administration of the test material had no related effects on clinical pathology test results. Administration of the control or test materials did not result in any macroscopic or microscopic lesions or findings at necropsy that were directly related to the test or control materials. The No Observance Effect Level (NOEL) for Ro41-0960 given as a single intravenous injection to female rats was 0.6 mg/kg.

Our IND application to carry out human PET studies was finally approved by the FDA on October 1, 1999

(b) obtain approvals for carrying out studies in human from both the Human Subjects Research Review Board (HSRRB) at the US Army Medical Research and Material Command, and from local IRBs, including our institute (BNL) and collaborating institute (SUNY at Stony Brook):

After received the IND from the FDA, we submitted a human study protocol and obtained approvals from the IRB of Brookhaven National Laboratory (BNL) on May 30, 2000, and from our collaborating institute (Stony Brook University, Hospital & Medical Center) on Jan. 20, 2000. We then submitted a package of documents to the HSRRB at the US Army Medical Research and Material Command on July 31, 2000 (see Appendix A). The first review by the HERRB was conducted on Sept. 13, 2000 and the second review was on Dec. 19, 2000. After all the revisions, the revised protocol and consent forms for both BNL and Stony Brook were finally pre-approved by the US Army Medical Research and Material Command on Jan. 16, 2001 (see Appendix B for the revised protocol and consent forms after reviewed by the HSRRB). A final approval won't be given until re-approvals from two IRBs on the revised protocol and consent forms are received by the HSRRB. The revised protocol and consent forms were re-approved by the IRB at BNL on April 17, 2001 (see Appendix C). Currently, we are waiting for the re-approval from Stony Brook.

(c) PET scanning in human breast cancer patients:

Once we receive the final approval from the HSRRB at the US Army Medical Research and Material Command, we'll recruit breast cancer patients from Stony Brook Hospital and carry out PET scans with [^{18}F]Ro41-0960 at BNL.

KEY RESEARCH ACCOMPLISHMENTS

(1). COMT activities in normal and abnormal human breast tissues from the same patient were compared. Preliminary results showed elevated COMT activities in the breast tumor tissues of all patients studied; the difference can be as high as a 26 fold increase. This will serve as a model prior to human studies.

(2). Our IND application to carry out human PET studies was approved by the FDA on October 1, 1999.

(3). The revised protocol and consent forms have been pre-approved by the HSRRB at the US Army Medical Research and Material Command, and re-approved by the IRB at BNL to carry out PET studies using [^{18}F]Ro41-0960 on breast cancer patients.

REPORTABLE OUTCOMES

Manuscripts:

Ding, Y-S. Fluorine-18 Labeled Biomolecules for PET Studies in the Neurosciences. J. Fluorine Chem. 101, 291-295 (2000).

Oral presentations (Invited lectures):

The Cancer Institute of Long Island at Stony Brook, School of Medicine, State University of New York at Stony Brook, New York, June 14, 2000. *(Novel Approach to Image Estrogen Metabolism in Breast Cancer Using PET)*

Scientific Committee, representative of Life Science, presenting one of the three labwide scientific talks to the Department of Energy Office of Science, Institutional Plan On-Site Review, July 24, 2000. *(PET Imaging of Chemistry in Living Systems)*

MRC Cyclotron Unit, Imperial College School of Medicine, Hammersmith Hospital, United Kingdom, October 16, 2000. *(Highlights of PET Studies at Brookhaven)*

Wolfson Brain Imaging Centre, University of Cambridge Clinical School, United Kingdom, October 18, 2000. *(Highlights of PET Studies at Brookhaven).*

DOE Biological and Environmental Research Nuclear Medicine Workshop, Williamsburg, VA, October 17-20, 2000. *(Radiotracer Chemistry and Technology Development and Applications).*

CONCLUSIONS

Our ability to assay COMT activities in human breast tissues sets the stage for us to examine the role of COMT in breast cancer, and will allow us to correlate between the radiotracer bindings and tissue COMT activities in the future PET imaging studies with [^{18}F]Ro41-0960. Preliminary results showing elevated COMT activities in the breast tumor tissues of all patients studied support our hypothesis that elevated uptake of [^{18}F]Ro41-0960 would be observed in breast cancer patients.

This novel approach to an extremely important medical problem goes beyond diagnosis in that it seeks to delineate the fundamental biochemical properties and molecular signatures of tumor cells. The benefit of this new knowledge would lead to a better understanding of the biochemistry of human breast cancer, suggest new therapies based on the tumor's molecular profile, and enhance the detecting and staging capabilities

of current diagnostic procedures. Unfortunately, obtaining all the approvals that are required to initiate the PET imaging studies in human has been far from straightforward. With all the effort and time we have invested on this project, and considering the seriousness of breast cancer and the need for reliable diagnostic procedures, we intend to see the scientific outcome of this project in spite of what hurdles are in front of us.

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Appendices:

A. **Initial submission to the HSRRB at US Army Medical Research and Material Command.**
B. **Revised protocol and consent forms after reviewed by the HSRRB.**
C. **Local IRB re-approval and revised consent forms after reviewed by the IRB at BNL.**

Appendix A

Chemistry Department

BROOKHAVEN
NATIONAL LABORATORY

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managed by Brookhaven Science Associates
for the U.S. Department of Energy

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July 31, 2000

Commanding General
U.S. Army Medical Research and Material Command
Office of the Deputy Chief of Staff for Regulatory Compliance and Quality
Human Subjects Protection, ATTN: MCMR-RCQ-HR
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Sirs:

I am writing to request that the enclosed protocol (Protocol Title: "PET Imaging of Estrogen Metabolism in Breast Cancer"; Principle Investigator: Yu-Shin Ding, Ph.D., Brookhaven National Laboratory (BNL); Proposal Log No.BC980045, HSP Log No. A-8956) to be reviewed by the Human Subjects Research Review Board (HSRRB). Attached are the following documents:

1. A copy of the Protocol following the ICH guidelines
2. A copy of our IRB approval memorandum
3. A letter from our IRB Chairperson with the following protocol information: (a) MPA number, (b) risk level that the IRB classified the protocol, (c) date of IRB approval, and (d) next continuing review date
4. This protocol has also been reviewed by University of Rochester; a copy of the approval letter is included
5. A copy of approval memorandum from our collaborating institute SUNY-Stony Brook
6. Consent forms (a) #710 and (b) #647 from BNL
7. Consent form from SUNY-Stony Brook
8. Case Report form
9. Curriculum vitae of all investigators plus the medical monitor
10. Document from the FDA specifying IND number
11. Scientific Review/Peer Review Approval
12. Protocol Submission Checklist

Please let me know if you have any questions. I look forward to hearing from you soon. Thanks.

Best regards,

Dr. Yu-Shin Ding
Senior Scientist

Item # 1

Brookhaven National Laboratory
Clinical Research Center
Upton, New York 11973

IRB PROCOTOL

IRB Title: PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960

Project (IRB) No.: 324

Principal Investigator: _____ Date: _____

Yu-Shin Ding

IRB 324 Protocol

Table of Contents

IRB Protocol: 324: PET Studies of Catechol-o-methyltransferase (COMT) with [18F]Ro41-0960

1. Study Rationale

A and B. Background and Preliminary Data:

It is well known that many breast tumors are associated with estrogen and there is evidence that the presence of catecholestrogens in breast tumors cause changes in the DNA which may lead to uncontrolled cell growth. Catecholestrogens are broken down by an enzyme called catechol-O-methyltransferase (COMT). COMT is known to be elevated in malignant breast tumors, and abnormal COMT genetics have recently been found in individuals with breast cancer. We have developed [^{18}F]labeled Ro41-0960, the first radiotracer for visualizing COMT with positron emission tomography (PET). The hypothesis that [^{18}F]Ro41-0960 can map COMT *in* vivo was demonstrated in baboon and mouse (Ding, et al., 1996; Ding, et al., 1997). The tracer uptake is highest in liver and kidney, which is consistent with high levels of COMT in these peripheral organs. Dose response curves and time course studies with PET for unlabeled Ro41-0960 in baboon indicated that the binding of [^{18}F]Ro41-0960 to COMT sites in periphery is saturable and sensitive to COMT inhibition (Ding, et al., 1998). A complementary *ex vivo* approach in which we correlated the radiotracer uptake with COMT activities in rodents further demonstrated the ability of [^{18}F]Ro41-0960 in mapping COMT activity *in vivo*. Recently, we have adapted our COMT enzyme assay method and performed studies in breast tumor tissue samples from cancer patients undergoing surgery (Ding, et al., 1999). COMT activities in normal and abnormal human breast tissues from the same patient were compared. Though COMT activities varied among subjects, preliminary results showed elevated COMT activities in the breast tumor tissues of all patients studied; the difference can be as high as 26 fold increase. This can be a potential signal to noise ratio for the PET studies in breast cancer that we have proposed.

Ding Y.-S., Gatley S. J., Fowler J. S., Chen R., Volkow N. D., Logan J., Shea C. E., Sugano Y., Koomen J. (1996) Mapping Catechol-*O*-methyltrans-ferase in vivo: Initial Studies with [^{18}F]Ro41-0960. *Life Sciences* **58**, 195-208.

Ding Y.-S., Sugano Y., Koomen J., Fowler J. S., Aggarwal D., Ferrieri R., Schlyer D. (1997) Synthesis of [^{18}F]RO41-0960, A Potent Catechol-O-Methyltransferase Inhibitor, for PET Studies. *J. Label. Cmpd. Radiopharm.* **39**, 303-318.

Ding Y.-S., Logan J.S., Gatley S.J., Fowler J.S., Volkow N.D. (1998) PET Studies of Peripheral Catechol-O-methyltransferase in Non-human Primates Using [^{18}F]Ro41-0960. *J. Neural. Transm.*, 105, 1199-1211.

Ding Y.-S. , Pyatt B. , Fowler J.S. , Volkow N.D. , Abumrad N., DeRisi.D. (1999) A Potential Use of [^{18}F]Ro41-0960, a Selective COMT Inhibitor, for PET Imaging of Estrogen Metabolism in Breast Cancer. *J. Nucl. Med.* **40**, 100P.

2. Design of the Trial

A. Introduction: Our studies have demonstrated that the activity of COMT, a soluble enzyme that catalyzes the O-methylation of various catechols including catecholestrogens, was significantly elevated in highly malignant human breast tumor tissue. The feasibility of mapping COMT *in vivo* with PET is supported by our recent baboon studies using [^{18}F]Ro41-0960. This proposed application involves the use of [^{18}F]Ro41-0960 and PET to localize and quantitate COMT in the human body as a marker for breast tumors.

The study will be carried out in breast cancer patients recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Patients slated to

undergo surgery will be scanned within four weeks of surgery and samples of tumor and normal tissue will be retained for histopathological characterization and for assay of COMT activity. Each subject will have one PET scan with [^{18}F]Ro41-0960. These studies will set the stage in developing a diagnostic tool to characterize the biochemical profile of breast tumors in human subjects. If successful, the benefit of this new method would lead to a better understanding of the role of COMT in the metastases of human breast cancer, as well as reducing the need for unnecessary breast biopsies and enhancing the staging capabilities of current diagnostic procedures. These studies may also provide information that suggests new treatments for breast cancer.

B. Hypothesis: Because COMT activity is significantly elevated in highly malignant human breast tumors and the uptake of [^{18}F]Ro41-0960 correlates very well with the activity of COMT in baboon and mouse, we hypothesize that an elevated uptake of [^{18}F]Ro41-0960 can be visualized with PET in breast cancer patients and that the elevated uptake will correlate with the elevated COMT activity in breast tumor.

C. Study Aims

i. Objectives: To test whether an elevated uptake of [^{18}F]Ro41-0960 can be visualized with PET in breast cancer patients.

ii. Specific aims and hypothesis:

a. To use PET to measure the uptake of [^{18}F]Ro41-0960 in breast cancer patients.

b. To compare the radiotracer uptake in the tumor breast with that in the normal breast from the same patient.

c. To compare COMT activity in the tumor breast tissue with that in the normal breast tissue from the same patient.

d. Hypothesis: see C2B

D. Eligibility criteria

i. Inclusion criteria:

1. positive needle biopsy, palpable breast tumor
2. Ability to understand and give informed consent
3. >18 years of age

ii. Exclusion Criteria:

1. pregnant
2. uncontrolled medical disease including

   diabetes, hepatic or renal disorders,

   Parkinson's or endocrine disease,

   psychiatric illness requiring antipsychotic drugs

3. prior history of radiation and/or chemotherapy
4. history of anaphylactic reactions
5. medications which may interfere with COMT activity
(for example, tolcapone or other COMT inhibitors)

E. Outcome Measures:

i. Primary:

1. A [^{18}F]Ro41-0960/PET scan
2. COMT activities in tumor breast tissue and normal breast tissue.

ii. Secondary: not applicable

iii. Descriptive measures: cardiac monitoring (all subjects).

F. Sample size and analysis plan: Breast cancer patients (n=20) will be recruited from Stony Brook who will be scheduled for their surgery within four weeks of their PET scan. For the analysis, we will compare the radiotracer uptake in the tumor breast with that in the normal breast from the same patient to determine if they are different. We will also compare COMT activity in the tumor breast tissue with that in the normal breast tissue from the same patient.

Power calculation: tumor characteristics are expected to vary and we can only estimate and not predict, the numbers to enter into a power calculation, nor do we know the normal variability. However, we will assume a 10% intersubject variability and a 20% difference in uptake between tumor and normal tissue. We need a sample size of 9 to achieve a significane of $p<0.05$. We want to recruit 20 patients because of anticipated difficulties in follow-through for patients who have just been diagnosed with breast cancer.

G. Recruitment;

i. Introduction: Breast cancer patients will be recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook.

ii. Resources: Jacki Judson-Eagle at Stony Brook serves as our recruiter. Naomi Pappas at BNL serves as our coordinator.

iii. Recruitment Plan: Breast cancer patients appearing to be eligible are then invited to BNL for prescreening and [^{18}F]Ro41-0960 /PET scan.

iv. Recruitment timeline: The rate limiting step is the identification and recruitment of breast cancer patients who meet inclusion criteria. We anticipate that the study will be completed in three years.

H. Randomization: not applicable

I. Masking: not applicable

J. Study flow sheet (see attached table).

K. Subject study flow sheet (see attached table)

3. Subject visits and treatment

A. Introduction

Breast cancer patients: this study takes one day. Each subject (breast cancer patient) has one PET scan with [^{18}F]Ro41-0960. Subjects are recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Subjects who have scheduled for their surgery will have initial screening and physical exams at Stony Brook to determine that the subjects meet inclusion/exclusion criteria prior to receiving the PET scan at BNL.

B. Screening visit: The screening visit at BNL will comprise a pregnancy test and brief physical exams to determine that the subject meets inclusion/exclusion criteria. Screening visit will take place the day of the PET scan.

C. Following visits: not applicable.

D. Study termination and close out: When the data is analyzed and a research manuscript is written and accepted for publication, then the study is terminated by filling out a termination form and submitting to the IRB.

E. Assessment timetable: necessary assessments are made on the day specified in the study flow.

F. Subject follow-up: A follow-up call is made the next working day by BNL after the study is completed to see if the subject has any study-related questions or problems. This is recorded in the medical record.

4. Description of examination procedures:

A. Rationale for selected eligibility criteria: Inclusion criteria are: a positive needle biopsy, palpable breast tumor, and no prior history of radiation and/or chemotherapy. Pregnant patients will be excluded from the study based on a pregnancy test (urine) on the day of the PET study. Subjects with any evidence of uncontrolled medical disease including diabetes, hepatic or renal disorders, Parkinson's or endocrine disease, psychiatric illness requiring antipsychotic drugs, or a history of anaphylactic reaction will be excluded. This eligibility criteria was chosen to minimize variables which may confound the interpretation of the study.

B. Cognitive assessment: during the physical examination, the physician will test the subject's orientation, cognition and judgment as to their ability to understand and give informed consent.

C. Descriptive measures: cardiac monitoring (all subjects).

D. Self-report measures: not applicable.

5. Data management

A. Data handling and collection: (see attachment including location of data)

B. Subject Accrual: In order to obtain an accurate count of new subjects enrolled for each study for reporting to the IRB, we will use multiple cross-checks following these steps. This applies to all PET protocols. We will obtain the subject accrual for each CIRC proposal by obtaining a printout of the new subjects from the present PET database capturing only new

subjects for the period requested by the IRB. We will check number and the PET run numbers against the records of N. Pappas (recruiter) and G-J Wang (physician) and reconcile this if there are differences.

C. Study documents (kept in Case Report Form)

PET Subject Information
Drug History (Doctor)
PET Run Data Sheet(s)
Study Flow Sheet
Inclusion/Exclusion Criteria
Cardiac Monitoring

D. Data entry: Physical examinations are administered by doctors or nurses and entered by hand. Information specific to the PET scan protocol is entered by the PET operator. The location of these records is described above in 5A attachment. Data in protocol specific forms is managed by Christopher Wong (ext 4989).

6. Study operations and quality assurance

A. Quality assurance: Details of procedures and documentation for critical measurements and materials are highlighted below.

During the course of the trial a Clinical Research Monitor will review the study progress, compliance to protocol and accuracy of the Case Report Forms in accordance with established BNL medical research monitoring procedures.

PET cameras: PET cameras are checked daily for stability of gantry electronics, photomultiplier tubes, and crystals using solid Ge-68 sources. This procedure is automated for the HR47+ and runs every morning before arrival of the subject. Results indicating the status of the gantry are printed automatically and report individual detector and total gantry deviations from values acquired during the last camera calibration and normalization. Acceptable ranges are reported along with the daily QC measure. A similar procedure and analysis is carried out manually on the CTI 931 camera. In this case only the total deviation of all detectors is in the gantry is reported. Acceptable ranges for QC measures are also indicated on the computer output. For both cameras a visual inspection of the QC sinogram is made before study protocols are continued.

After stability testing, radioactivity from a low activity (< 1 microCurie) Ge-68 "aliquot" source is acquired. Both singles (HR+ only) and coincidence counts are recorded in both 2D and 3D (HR+ only) acquisition modes.

All results from daily QC tests are recorded in both the camera log book and the Building 906 Quality Assurance Log Book. PET cameras are calibrated and normalized according to standard procedures for Building 906 as dictated by daily QC test results or under special circumstances including detector replacement, software upgrade, etc. Calibrations and normalizations are carried out using uniform Ge-68 phantoms that have been previously calibrated using 18F-flouride.

Picker Well Counter: Well counter stability is determined daily using a sealed calibrated radioactivity source (Ge-68 and/or Cs-137). Source counts are recorded daily on run sheets and in the PET Clinical Laboratory Quality Assurance Log. Absolute counter efficiency is determined bi-annually according to standard procedures using 18F-fluoride and liquid

scintillation counting. Results are recorded in a calibration notebook stored in the Building 901 Radiotracer Laboratory supervisor's office.

Capintec Dose Calibrator: The Capintec dose calibrator is calibrated every 6 months according to standard procedures using mCi levels of 18F and/or 11C radioactivity. Previous and new calibrator setpoints for measuring 18F and 11C are recorded in a calibration log book located in the Radiotracer Laboratory supervisor's office.

Radiotracers: All radiotracer quality assurance and batch production records are stored in notebooks in the GMP lab in Building 901. Sterility and pyrogenicity records for each delivery of radiotracer are kept in Room 383; Building 555 (Chemistry). Radiotracers undergo a battery of appropriate quality assurance tests. All results must lie within established acceptable ranges. Acceptance of radiotracer is verified by a designated chemist's signature in the batch records.

B. Subject information and informed consent: The subject fills out a Subject Information Form containing demographic information. The subject also fills out a medical History form which is reviewed by the physician. The physician meets with the subject and explains the procedures in the study. The subject is asked to sign the consent forms after the procedures have been explained. Signed consent forms are kept in the Medical Record.

C. Drug dosage and supply: C-11 and F-18 labeled radiotracers are prepared each time they are needed because of the short half life of carbon-11 (20.4 minutes) and F-18 (110 minutes). Quality control records for each batch are kept in lab 113 of bldg 901 and in lab 383 of bldg 555 as described in 6A. Once a radiotracer is delivered to the PET Imaging Laboratory, the dose specified in the IRB Proposal is withdrawn into a syringe and counted in a dose calibrator and the time is recorded on the PET run data sheet. It is then injected and the time of injection is recorded. The empty syringe is counted again and the time recorded to obtain an accurate measure of the dose which the patient received. The physician also logs the dose and time that it is injected in the Medical Record on the form "Clinical Report of PET Study" and in the Internal Radioisotope Summary Sheet in the subject's medical record.

D. Monitoring for medication compliance and adverse effects. Cardiac monitoring is carried out during the study. Close monitoring of the subject during the study and the follow-up call will pick up adverse events if they occur.

E. Unscheduled termination/removal of subject: If a subject withdraws early from the study or if the physician determined that he/she does not meet eligibility criteria after enrollment in the study (for example, if a subject has a positive urine pregnancy test during the screening visit for the PET study), then the subject is withdrawn and the reason noted in the chart.

7. References (see 1A above)

2 J. Study Flow Sheet

1. Subject (a breast cancer patient) is recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Subject who has scheduled for her surgery will have initial screening and physical exams at Stony Brook to determine that she meets inclusion/exclusion criteria prior to the day she receives the PET scan. The subject is scanned before surgery.
2. Subject arrives at CRC (Clinical Research Center) / PET for initial BNL screening.
3. Subject signs consent 647 and fills out the Subject Identification Form.
4. Subject receives laboratory tests.
5. Subject receives a brief history/physical examination to assess ability to understand and give consent and to determine if he/she meets inclusion criteria.
6. If inclusion criteria are met, the study consent (#710) is administered. At this point the subject is enrolled.
7. The hand is warmed. The arterial and venous catheters are inserted.
8. Subject is positioned in the PET and has a transmission scan performed.
9. Cardiac monitoring is performed during the study.
10. The radiotracer ([^{18}F]Ro41-0960) is injected and scanning commences for 64 minutes. Blood samples are taken and analyzed during this time for 18F activity and plasma analysis.
11. The arterial and venous catheters are removed
12. At the end of the scanning period the subject is asked to urinate.
13. The subject is given a meal.
14. The subject is paid and given a comment form.
15. The subject receives a follow-up 12 lead EKG at CRC after the study and then discharged.
16. The subject receives a follow-up call on the next working day.

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT.

2K. Subject Study Flow Sheet

Procedure	Prescreen Visit (Stony Brook)**	Visit (BNL)	Surgery Visit (Stony Brook)
informed consent (SUNY)	x		
informed consent (#647)		x	
informed consent (#710)		x	
EKG	x	x (after PET scan)	
blood lab	x		
review-inclusion/exclusion	x	x	
medical history	x		
complete physical exam	x		
pregnancy test	x	x	
brief physical exam		x	
drug history	x	x	
PET subject information		x	
PET scan		x	
tissue samples			x***
volunteer fee paid		x	
Follow-up call		x*	

* next working day

** records are maintained at Stony Brook. A copy is sent to BNL and maintained in the medical record.

*** tissue samples are obtained at surgery, frozen and transferred to BNL for analysis at a later date.

5A. Data Handling and Collection

Summary of data types and location for all Human PET experiments

Radioactivity Measurements

PET Image Data

1. Ecat 931 Tomograph

Electronic records (image files) are stored in an optical disk library located in Room 3 and Room 8 in Building 906. Hard copy records of recent run sheets are stored in the Room 3 in Building 906. Older run sheets are archived in Room 9. All raw and reconstructed data are also stored on 8mm tape in Room 9.

2. Siemens Hr47+ Tomograph

Electronic records (volume files) are stored on hard disks mounted to a Sun Ultra60 workstation named ultrabrain3d.pet.bnl.gov in Room 8 in Building 906. Hard copy records (run sheets) are stored in Room 3 and Room 9 in Building 906. All raw and reconstructed data are also stored on 4mm tape in Room 9.

Plasma concentration

Electronic records (cnt and vol files) are stored on a hard disk mounted to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records of plasma data are stored in Room 3 (recent) and Room 9 (archived).

Metabolite correction

Electronic records (met files) are stored on a hard disk connected to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records are stored outside room 134-I in Building 901W in metal filing cabinets.

Urine

Urine toxicology screen is kept in the Medical Record. Urine radioactivity measurements, if obtained, are recorded on the PET blood lab data sheet.

Injected Dose

Electron records (lab files) are stored on a hard disk mounted to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records (PET blood lab data sheets) are stored in Room 3 (recent) and Room 9 (archived).

A. Region of Interest (ROI) data

1. Ecat 931 Tomograph

Electronic records (ROI files) are stored on a hard disk mounted to the Sun workstation named viewbrain.pet.bnl.gov in Room 8 in Building 906.

2. Siemens Hr47+ Tomograph

Electronic records (ROI files) are stored on a hard disk mounted to a Sun Ultra60 workstation named ultrabrain3d.pet.bnl.gov in Room 8 in Building 906.

B. Blood and Urine analysis

Hard copy records of blood or urine measurements are stored in locked file cabinets in Rooms 5-33 and 5-31 in Building 490.

I. Cardiovascular Data

Hardcopy records are stored in locked file cabinets in Rooms 5-33 and 5-31 in Building 490.

II. Plasma analysis

Hardcopy records are stored in locked file cabinets in Room 5-33 and 5-31 in Building 490.

Electronic source file machine:directory key:

Source file location is identified by the workstation's official Internet Protocol name (IP name) followed by the exact Unix filesystem separated by a colon (**machine.name:filesystem**)

1. **931 Image files (**.img*)** - viewbrain.pet.bnl.gov:/data1 (when optical is mounted)
2. **HR47+ Volume files (**.v*)** – ultrabrain3d.pet.bnl.gov:/home/data3 or /home/data4

Data is normally accessed through CTI's Ecat v. 7.2 software and database using the workstations ultrabrain3d.pet.bnl.gov and u2brain.pet.bnl.gov

3. **Plasma radioactivity files *(*.cnt and*.vol)*:**

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. rcs)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0 or /usr2/data0/xxx where xxx is the study code (e.g. ccs).

4. **Dose, plasma glucose, and scanning information (**.lab files*):**

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. mrh)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0

or /usr2/data0/xxx where xxx is the study code (e.g. ras)

5. **Metabolite correction files (**.met*):**

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. nas)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0

or /usr2/data0/xxx where xxx is the study code (e.g. omh). Metabolite files are also stored on the PC named hotlab.pet.bnl.gov in Building 901.

6. **ROI files *(*.roi and *.txt)*:**

931 (.roi*)** – viewbrain.pet.bnl.gov:/petsys/xxx or /petd/xxx or /petd1/xxx where "xxx" is the investigator ID code (e.g. jsf) or other investigator defined project code.

HR47+ (.txt*)** - ultrabrain3d.pet.bnl.gov:/hrpd/xxx where "xxx" is the investigator ID code (e.g. sld)

Item 2

BROOKHAVEN NATIONAL LABORATORY
MEMORANDUM

DATE: May 30, 2000

TO: Yu-Shin Ding

FROM: M.C. Bogosian, Chairman, Institutional Review Board (IRB)

SUBJECT: **IRB Protocol 324** "PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960"

At the 05/23/00 IRB meeting, the request to restart the above protocol was approved.

Approval by the CRC Manager is required before work may begin under this protocol.

This protocol is approved until 11/02/00. This approval is given only for the protocol submitted; any changes must be approved by the IRB prior to being implemented.

You should be aware that all research outlined in this protocol must be carried out under approved Experimental Safety Review(s) (ESR) and that this application must contain the same information as that listed in the approved ESR(s). You must be aware that it is your responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

Investigators must report any unanticipated problems promptly to the IRB.

IRB

M.C. Bogosian
B.D. Breitenstein
S. Mendelsohn
H.L. Atkins
A.Z. Diaz
D.J. Schlyer
R. Ferrieri
C. Schaefer
E.T. Lessard
J. Van=t Hof
T. Butcher
J. Lombardo
J. Gisondo
E. Lowenstein
J. Taylor
D. Dunn
E. Sokol
E. Weiss
K. Waterman

MCB:dm
IRB Form 010: Approved 08/04/98; Revised 06/01/99

Office of Research Administration

Item 3

BROOKHAVEN
NATIONAL LABORATORY

managed by Broo
for the

July 24, 2000

Commander
US Army Medical Research and Material Command
Attn: MCMR-RCQ-HR
504 Scott Street
Fort Detrick, MD 21702-5012

Dear Commander:

Brookhaven National Laboratory (BNL) has a Multiple Project Assurance (MPA) with the National Institutes of Health (M-1313-XB).

The IRB Protocol 324 entitled "PET Studies of Catechol-O-Methyltransferase (COMT) with [^{18}F]Ro-41-0960", Principal Investigator YuShin Ding, has been reviewed by the BNL Institutional Review Board and classified as greater than minimal risk. The protocol was granted initial approval on November 2, 1999 and its next continuing review must be completed prior to November 2, 2000.

Please contact me if you have any questions.

Respectfully submitted,

Margaret C. Bogosian
Chair, IRB

MCB:dm

UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

EASTMAN DENTAL CENTER
OOL OF MEDICINE AND DENTISTRY
SCHOOL OF NURSING
STRONG MEMORIAL HOSPITAL
IVERSITY MEDICAL FACULTY GROUP
NICAL RESEARCH INSTITUTE

May 17, 2000

Yu-Shin Ding, MD
Brookhaven National Laboratories
Building 555A
Upton, N.Y. 11713

Re: IRB Protocol 324

Dear Dr. Ding:

Please be advised that I have concluded my review of the above protocol and newly developed Case Report Forms and find them to be compliant with Good Clinical Practice (GCP) standards. I have also established that an acceptable subject accrual/tracking system is in place and that the Investigator file contains all of the essential elements as required by GCP and internal BNL policy and procedures. This letter is issued with the proviso that you will present the IRB an addendum to your current IRB summary document. Please contact me if you have any questions or concerns.

Sincerely,

Tim Hackett

Timothy J. Hackett
Manager, Quality Assurance and Project Management
University of Rochester, Clinical Research Institute

601 Elmwood Avenue, Box 706
Rochester, New York 14642
(716) 273-4127 Fax: (716) 242-4862

Item 5

STONY BROOK
STATE UNIVERSITY OF NEW YORK

Office of the Vice President for Research
Research Informatics and Compliance

TO: Margaret Kemeny

FROM: Judy Matuk, University Coordinator for Research Compliance

SUBJECT: Approval for Research Involving Human Subjects (APP)

DATE: 01/20/2000

The project referenced below was reviewed by the Committee on Research Involving Human Subjects (CORIHS: Assurance #M1036-01) and approved on: 1/14/00 . Attached is a copy of the approved consent form and the human subjects application with the endorsement of CORIHS and the Institution. This approval is valid for one year.

Federal regulations require that:

1. all research involving human subjects be reviewed at least once annually. You will be sent an application for renewal of CORIHS approval two months prior to the anniversary date.
2. any modifications in the project as approved by this Committee involving changes in the selection of subjects, the means for obtaining informed consent, the wording of the approved consent form(s), or in the risk to subjects be sent to the Committee for review and approval prior to initiation.
3. the Principal Investigator must keep consent forms with patient/subject signatures in a locked file to ensure confidentiality.

This approval is subject to recall if at any time the conditions and requirements of the CORIHS are not met. This is for the protection of all parties: the subjects, the investigators, the University and CORIHS.

Description of Study:

Project ID: 19993755

Approval Period: 1/14/00 - 1/13/01

Project Title: PET Imaging Of Breast Cancer Using (18F) Ro41-0960

Consent form 710
(Brookhaven Lab) (Revised on May 12, 2000)

Item 6a

Consent Form Number: 710

Date of First Approval: 11/99

Date of Most Recent Approval 11/99

Date of Expiration: 11/00

CLINICAL RESEARCH CENTER
MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973-5000
INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Title of Project: PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960
Funding: Department of Defense, Department of Energy

1. **I am invited to participate in a research project. The overall purpose of the research is:**

Catechol-O-methyltransferase (COMT) is a natural enzyme in the body that is sometimes found in greater amounts in certain breast tumors. The purpose of this study is to determine whether the larger amounts of COMT can be seen in breast cancer with Positron Emission Tomography (PET), a medical imaging method similar to a camera, and whether this information can be of value in breast cancer diagnosis and treatment. The procedure will involve PET scanning with a tracer called [18F]Ro41-0960, which links itself with the COMT already in the tumor. If I have breast cancer and am scheduled to undergo surgery, I will have a PET scan before the surgery. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which is removed during the surgery. If PET and the experimental tracer [18F]Ro41-0960 provide diagnostic information, it could reduce the need for unnecessary breast biopsies and make current diagnostic procedures better. This study may also provide knowledge which may suggest new treatments for breast cancer.

2. **My participation will involve the following:**

The general PET Procedure is described in the PET Brochure which I have been given.

Arterial and Venous Catheterization: It is necessary to place a catheter (a small tube) in a vein in my arm for the radiotracer injection. It is also necessary to obtain either arterialized venous or arterial blood samples for some of the measurements needed in this work. To obtain these blood samples, I will either have a catheter placed in a vein in my hand (for arterialized venous samples) or an catheter placed in a radial artery in the wrist area (for arterial samples). If blood samples are to be taken from an artery, the physician will perform a painless test to determine whether the arteries that supply blood to the hand are functioning. The test will consist of the closing my hand and having the physician press down on my radial artery. I will then be asked to open my hand, and if it appears that blood is not flowing to my hand through the ulnar artery, the investigators will not proceed with the study. For arterialized venous samples, my hand will be warmed after the catheter is in place to promote the mixing of arterial and venous blood, a condition which is needed for the blood sampling, which will occur during the PET scan. The placing of arterial catheters and their use is generally more painful and uncomfortable than is the case with intravenous catheters. However, to relieve pain, a dose of xylocaine will be given by a small needle under the skin before the catheterization. The use of an arterial catheter also involves some additional risk of temporary interference with arterial blood flow to the hand involved. Such complications are uncommon and can be controlled by the physician supervising the study. During these

procedures, the catheter may be in place for up to seven hours.

Preparation for the PET scan: As part of the evaluation procedure I will undergo a physical examination which will include a medical history. This will also include lab testing of blood and urine chemistry and a test for pregnancy (if I am a female subject of childbearing age). The investigators may also ask for my alcohol and drug history. Electrocardiogram (EKG) may also be performed to ensure that there are no problems with the functioning of the heart. I will be asked to refrain from taking any other drugs while I am participating in this study unless I receive permission from my physician.

PET Scans: Before and during scanning I will wear a heart monitor to record my heart rate and blood pressure. Before the injection of the radiotracer, the breast area will be scanned two or three times, for about 5 minutes each while it is surrounded by a ring containing a photon-emitting substance. I will be expected to lie still during the PET scanning.

This study will involve the administration of less then 5 millicuries (mCi), a measurement of radioactivity, of [^{18}F]Ro41-0960, an experimental tracer. The scan will be of the breast area and require about 64 minutes. At the end of the study a second 12 lead EKG will be obtained. I will be taken to urinate at the end of the scanning to reduce the radiation exposure to my lower abdominal region. I may be asked to be rescanned 1 hour later for 10-20 minutes.

Throughout the procedure, the investigators will be obtaining blood samples to measure concentration of radiotracer in blood. A total of no more than 60 cc (4 tablespoons) of blood will be removed for any single injection of the radiotracer. Blood samples may also be analyzed for other measures which the investigators need for the studies.

3. **My participation is expected to have the following duration:**

Six to eight hours for each day of participation. I am only scheduled for one day at this time, but if the results from the preliminary studies are promising or my breast cancer returns, I may be asked to return for a second scan.

4. **There are certain risks and discomforts that may be associated with this research:**

Catheter Placement for Injection and Blood Sampling: The PET study requires venipuncture for radiotracer injection and arterial or arterialized venous catheterization and its attendant risks. Arterial catheterization has the following rare but possible complication: pain during placement of the catheter; a risk of bleeding at the skin puncture site; the possibility of local infection; temporary or permanent impairment of the blood supply to portions of my hand, which could lead to loss of fingers. Pain during the placement of the catheter is minimized by the use of a local anesthetic which will be injected at the site of skin puncture. The chance of excessive bleeding from the catheter site will be minimized by a prolonged application of pressure. The risk of infection will be minimized by the use of local antiseptic measures prior to catheter placement. The catheter itself is received in sterile condition. Whenever blood is removed or a substance is injected by venipuncture, there is minor discomfort and a slight possibility of local bleeding in the tissues. I should refrain from moderate to heavy exercise of the hand where the catheter was placed for at least 3 days after the study.

Adverse reactions: Because of the short half life of F-18, the radiotracer cannot be tested for sterility and freedom from fever producing compounds before it is administered. However, the system for production is checked frequently and consistently produces a product free from bacteria and fever producing compounds. No allergic reactions caused by contamination of the radiotracer have been encountered.

All of the radiotracers are administered in very small chemical doses (less than 50 micrograms per radiotracer injection). This dose is below that which will cause a pharmacological or addictive effect.

Radiation Exposure: The radiation dose from this procedure is 445 mrem. For comparison, the average background radiation in the United States is 300 mrem per year. Example radiation doses from standard clinical

procedures are: Bone scan – 440 mrem; thallium stress test - 4400 mrem. Cancer can be caused by large doses of radiation; however radiation-induced cancer has not been observed in persons exposed to low doses such as in this study. The investigators estimated the risk of radiation-induced cancer from such low doses by scaling the risk from high dose results. Because the normal lifetime risk of fatal cancer is about 20% in the United States, the additional theoretical risk from this procedure is so small that it is not likely to alter the overall chances of cancer occurrence.

5. **The following alternatives are available for obtaining the same knowledge as will result from this study:** There are no alternative procedures which can be expected to give the same information as is expected from this study.

6. **The possible benefits to me/and or to society from this research are:** As a research patient of the Clinical research Center, Brookhaven National Laboratory, I am asked to participate in procedures and studies which are not established medical practice. These studies are undertaken to learn more about the human body in health and disease; to discover and evaluate new methods of diagnosis and treatment of certain diseases; to examine the effectiveness of current methods of treatment in hope that a better understanding will lead to more effective control or even its eradication.

There is no direct benefit to me, however, information gained from this study may help development of a better understanding and diagnosis of breast cancer.

7. **Brookhaven National Laboratory will take all reasonable measures to protect the confidentiality of my records and my identity will not be revealed in any publication resulting from this study.** This includes information disclosed by me in completing any research project questionnaire or information obtained from me during participation in this research project. There is a possibility that my medical record, including identifying information, may be inspected by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. A representative of the sponsor, the Department of Defense, may also inspect these records.

8. **My participation is totally voluntary** and I am free to withdraw from the study at any time and to discontinue participation without prejudice. If I am an employee here at Brookhaven, the investigators want to be especially clear on this point. My refusal to participate or continue will not be questioned by the investigators, nor will it be discussed further with anyone else. Furthermore, if I am directly supervised by the Principal Investigator (Y.S. Ding) or the Responsible Physician (N.D. Volkow) I may not participate in this study. Also, if I participate in this study and I am a Brookhaven employee, I must take vacation time for the time I participate in this study.

The investigator may withdraw me from this research study if at any time circumstances arise which warrant doing so. I will be given a copy of the Participants Bill of rights.

9. **If I receive a physical injury resulting from the research procedures,** medical treatment will be provided free of charge; however, monetary compensation is not available.

10. **If it is discovered that I have some unrelated medical illness** during my participation in this project, I will be informed and advised to seek appropriate medical care. BNL will not compensate me for any underlying condition discovered during the study.

11. **Other institutions may be collaborating with Brookhaven** and therefore I may be contacted by the

following institutions in order to arrange for appointments: None.

12. **I will receive a volunteer fee:** I will receive $100.00 for each day of participation in this study.

13. If I have any questions or concerns regarding this study, or if any problems arise, I should call the Responsible or the Participating Physician. I may also direct questions about my rights as a research subject to the Chief of Staff, Brookhaven Clinical Research Center.

Responsible Physician: Nora D. Volkow Phone: 631 344-3335

Participating Physician: Gene-Jack Wang Phone: 631 344-3608

Chief of Staff: Aidnag Diaz Phone: 631 344-2773

I have read this consent form and have been given the opportunity to ask questions. I understand that I will also be given a copy for my records. I hereby consent to participate in this procedure.

PARTICIPANT'S NAME: _____

SIGNED BY: _____

(Patient and, when necessary, legal guardian) (Date)

WITNESS: _____

(Date)

I, the undersigned, herewith affirm that I have explained the above to _____ and am willing to answer further inquiries.

_____ _____(Date)

Consent Form 647
(Brookhaven Lab)

Item 6

Consent Form Number: 647
IRB Protocol Number: All PET Protocols
Date of First Approval: 08/06/97
Date of Most Recent Approval: 08/01/00
Date of Expiration: 08/01/01

CLINICAL RESEARCH CENTER
MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973-5000

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Title of Project: LABORATORY TESTING FOR PET RESEARCH STUDY

1. **You are invited to participate in a research project** which will require a series of tests to be given prior to your PET scans to determine your eligibility to participate in this study. Results from these tests may disqualify you from acceptance as a volunteer for a PET protocol.

2. **Your participation will involve the following:**

Urine Test: You will be asked to give a sample of urine when you arrive. A urine test will be performed to measure the possible presence of drugs including marijuana, cocaine, PCP, benzodiazepines (such as Xanax, Valium, Ativan), amphetamines (such as Dexedrine), opiates (such as Vicodin, Demerol) and barbiturates (such as Seconal, Nembutal). This test is performed to ensure that you have not taken drugs prior to the PET procedure, since this would interfere with the results obtained. This test will be repeated if you return on another day.

A positive urine drug screen will exclude you from this study unless otherwise noted.

Pregnancy Test: If you are female and are of child bearing potential a sample of your urine will be collected to determine if you are pregnant This test may be repeated each day of the PET scanning.

A positive pregnancy test will exclude you from this study.

Electrocardiogram (EKG): An EKG (a recording of the electrical activity of your heart) will be performed to determine if there are problems with the functioning of your heart.

Blood Chemistry: About 25 ml (6 teaspoons) of blood will be drawn from a vein in your arm using a needle. This is done to check if your blood cell counts and chemistry are within the normal ranges. We will also check to see if you have had recent or past exposure to Hepatitis B or C.

Breath Test for Carbon Monoxide: This test will show if you have smoked recently or been with people who smoke. You will be asked to take a deep breath in and to hold this for as long as possible and then to breathe out slowly and steadily through the mouthpiece of the measuring device.

Tobacco Questionnaire: You will be asked eight questions about your smoking habits to assess your degree of dependence on tobacco smoking.

Saliva/Alcohol Test: A doctor or nurse may take a sample of your saliva and test it for alcohol. The saliva sample will be taken with a cotton swab which is swabbed around your mouth (cheek, gums and under your tongue) for 30-60 seconds until it is thoroughly wet. The doctor or nurse will then analyze your saliva for the

presence of alcohol. This test may be done during your screening visit and may also be performed weekly to monitor your abstinence from alcohol, if the study requires a period of abstinence.
A positive alcohol test will exclude you from this study unless otherwise noted.

3. **Your participation is expected to have the following duration:** Laboratory testing and EKG will take about 30 minutes. The breath test, mental assessment and tobacco questionnaire will take about 15 minutes.

4. **There are certain risks and discomforts that may be associated with this research:**
Blood Withdrawal: The blood drawing is of minimal risk; however, it can lead to certain discomfort. Also, in some instances, there may be small bruises where the needle was inserted and a few drops of blood may leak out after the needle is removed.

5. **The following alternatives are available for obtaining the same knowledge as will result from this study:** None.

6. **The possible benefits to you/and or to society from this research are:**
As a research subject of the Clinical Research Center, Brookhaven National Laboratory, you are asked to participate in procedures and studies which are not established medical practice. These studies are undertaken to learn more about the human body in health and disease; to discover and evaluate new methods of diagnosis and treatment of certain diseases.
There may be a benefit to you from the knowledge gained from the results of these tests. There may be no benefit to you from the tests.

7. **Brookhaven National Laboratory will take all reasonable measures to protect the confidentiality of your records and your identity will not be revealed in any publication resulting from this study.** This includes information disclosed by you in completing any research project questionnaire or information obtained from you during participation in this research project. There is a possibility that your medical record, including identifying information, may be inspected by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. A representative of the funding institution of this study may also inspect these records.

8. **Your participation is totally voluntary** and you are free to withdraw from the study at any time and to discontinue participation without prejudice. If you are an employee here at Brookhaven, the investigators want to be especially clear on this point. Your refusal to participate or continue will not be questioned by the investigators, nor will it be discussed further with anyone else. If you are directly supervised by the Principal Investigator (J.S. Fowler) or the Responsible Physician (N.D. Volkow), you may not participate in this study. Also, if you participate in this study and are a Brookhaven employee, you must take vacation time for the time you participate in this study. You will be given a copy of the Participants Bill of Rights.

9. **If you receive a physical injury resulting from the research procedures,** medical treatment will be provided free of charge; however, monetary compensation is not available.

10. **If it is discovered that you have some unrelated medical illness** during your participation in this project, you will be informed and advised to seek appropriate medical care. BNL will not compensate you for any underlying condition discovered during the study.

11. **Other institutions may be collaborating with Brookhaven** and therefore you may be contacted by the

following institutions in order to arrange for appointments: None.

12. **You will receive a volunteer fee:** You will receive $50 if you undergo all the laboratory tests and $25 if you only undergo urine testing. If you claimed to be drug-free and your urine tests are positive for drugs, you will not receive a volunteer fee. If you are selected to participate in the PET study today, you will receive an additional $50 for the day. You will be informed of the results of these tests. If you withhold any information during the telephone screening about any medications you may be taking (even therapeutic medications which you are using to treat illnesses that you may have), you will not receive the volunteer fee for the Laboratory testing. If this is discovered after you have been enrolled as a subject for a PET study, you will not receive a volunteer fee for the PET study.

13. If you have any questions or concerns regarding this study, or if any problems arise, you should call the Responsible or the Participating Physician. You may also direct questions about your rights as a research subject to the Clinical Research Center (CRC) Physician.

Responsible Physician: Nora D. Volkow Phone: 631 344-3335

Participating Physician: Gene-Jack Wang Phone: 631 344-3608

CRC Physician: Jack Coulehan Phone: 631 344-3672

You have read this consent form and have been given the opportunity to ask questions. You understand that you will also be given a copy for my records. You hereby consent to participate in this procedure.

SIGNED BY: _____

(Subject and, when necessary, legal guardian) (Date)

The undersigned herewith affirms that they have explained the above and are willing to answer further inquiries.

_____ _____(Date)

Consent Form
(SUNY-
Stony Brook)
Item 7

Consent Form

TITLE: Pre-Op PET Studies of Catechol -O- Methyltransferase (COMT) with (18F) Ro41-0960 for Patients with Breast Cancer

PRINCIPAL INVESTIGATOR: Margaret Kemeny, M.D., Nora Volkow, M.D., Yu-Shin Ding, PhD

You are being asked to participate in a research study.

PURPOSE: The purpose of this study is to determine whether a certain enzyme, COMT, which is elevated in certain breast tumors, can be seen in the breast with PET, a medical imaging method. If so, this information may be of value in breast cancer diagnosis and treatment.

The procedure will involve PET scanning with a radioactive tracer called [18F] Ro41-0960, which attaches to COMT. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which was removed from your breast. If PET and [18F] Ro41-0960 provides diagnostic information, it could reduce the need for unnecessary breast biopsies and enhance the staging capabilities of current diagnostic procedures. This study may also provide knowledge, which may suggest new treatments for breast cancer.

PROCEDURES: If you decide to be in this study you will have a PET scan, blood work and an evaluation, at Brookhaven National Laboratory, within 4 weeks before your surgery.

Preparation for the PET scan: As part of the evaluation procedure at Brookhaven National Laboratory, you will undergo a physical examination which will include a medical history. This will also include lab testing of blood (approximately 2 tablespoons) and urine chemistry and a urine test for pregnancy (if you are a female subject of childbearing age). The investigators may also ask for your alcohol and drug history. In some subjects, an electrocardiogram (EKG) may also be performed to ensure that there are no problems with the functioning of the heart. You will be asked to refrain from taking any other drugs while you are participating in this study unless you receive permission from your physician.

PET Scans: Before and during scanning you will wear a heart monitor to record your heart rate and blood pressure. Before the injection of the radiotracers, the breast area will

be scanned two or three times, for about 5 minutes each while it is surrounded by a radioactive substance. You will be expected to lie still during the PET scanning.

This study will involve the administration of radioactive [18F] Ro41-0960. The scan will require about 64 minutes. You will be asked to urinate at the end of the scanning to reduce the radiation exposure to your lower abdominal region. There is a possibility that you may be rescanned 1 hour later for 10-20 minutes.

Arterial and Venous Catheterization: It is necessary to place a catheter in a vein in your arm for the radiotracer injection. It is also necessary to obtain either arterialized venous or arterial blood samples, for some of the measurements needed in this work. To obtain these blood samples, you will either have a catheter placed in a vein in your hand (for arterialized venous samples) or a catheter placed in a radial artery in the wrist area (for arterial samples). For arterialized venous samples, your hand will be warmed after the catheter is in place to promote the mixing of arterial venous blood, a condition which is needed for the blood sampling, which will occur during the PET scan. If blood samples are to be taken from an artery, the physician will perform a painless test to determine whether the arteries that supply blood to the hand are functioning. Only if the test is normal will the investigators proceed with the study. The placing of the arterial catheters is generally more painful and uncomfortable than is the case with intravenous catheters. A dose of xylocaine will be given under the skin by a small needle before the catheterization to relieve pain. During these procedures, the catheter may be in place for up to 7 hours.

Throughout the procedure, the investigators will be obtaining blood samples to measure concentration of radiotracer in blood. A total of no more than 60 cc (4 tablespoons) of blood will be removed for any single injection of the radiotracer. Blood samples may also be analyzed for other measures, which the investigators need for the studies.

Your participation is expected to be about 6-8 hours for each day of participation. We may ask you to repeat this study in the future if your breast cancer recurs.

RISKS: Catheter Placement for Injection and Blood Sampling: Arterial catheterization has the following rare but possible complications: pain during placement of the catheter, a risk of bleeding at the skin puncture site, the possibility of local infection, temporary or permanent impairment of the blood supply to portions of your hand. Pain during the placement of the catheter is minimized by the use of a local anesthetic, which will be injected at the site of skin puncture. The chance of excessive bleeding from the catheter site will be minimized by a prolonged application of pressure. The risk of infection will be minimized by the use of local antiseptic measures prior to catheter placement. The use of an arterial catheter also involves some additional risk of temporary interference with arterial blood flow to the hand involved. Such complications are uncommon and can be controlled by the physician supervising the study. In addition, the placement is done by a trained physician and we exclude any subjects with peripheral artery disease and/or in whom there is not a palpable ulnar artery. Whenever blood is removed or a substance is injected by needle into a vein, there is minor discomfort and a slight possibility of local

bleeding in the tissues, bruising and fainting. The injection of the anesthetic, xylocaine, may be painful.

You should refrain from moderate to heavy exercise for a few days following this procedure, especially using the hand where the catheterization was performed.

Adverse allergic reactions: Because of the short half-life of F-18 (110 minutes), the radiotracer cannot be tested for sterility and freedom from fever producing compounds before it is administered. However, the system for production is checked frequently and consistently produces a sterile product, free from fever producing compounds. No such allergic reactions have been encountered. In addition, all of the radiotracers are administered in very small chemical doses (less than 50 micrograms per radiotracer injection). This dose is below that which will cause a pharmacological effect.

Radiation Exposure: The total amount of radiation exposure you will receive from this study (1 injection) is 445 mrem (effective dose equivalent). For comparison the average radiation background in the U.S. is about 300 mrem/year. Radiation doses from standard clinical procedures are: Bone scan- 440 mrem; Thallium stress test – 4400 mrem. A potential side effect of radiation is the induction of cancer. However, no harm in a human individual or in a large population exposed at doses as low as that delivered in this procedure has been observed. Thus the estimation of the risk of harm can be obtained only by extrapolation from much higher doses. The calculated risk is small and would raise the "normal" risk of lethal cancer, which is about 20% to 20.01%.

If you are a woman of childbearing potential you should practice effective birth control while participating in this study. If you should become pregnant, you must inform your doctor immediately. Exposure to radiation is harmful to a fetus.

BENEFITS: There may be no direct benefit to you, however, information gained from this study may help development of a better understanding and diagnosis of breast cancer.

PAYMENT TO YOU: You will receive $ 100.00 for the day of participation in this study at Brookhaven National Laboratory as well as any traveling expenses.

COSTS TO YOU: There will be no charge to you or your insurance company for any treatment or care that you receive as part of this study.

CONFIDENTIALITY: The following procedures will be followed in an effort to keep your personal information confidential in this study. Your identity will be coded, and all data will be kept in a secured, limited access location. Your identity will not be revealed in any publication or presentation of the results of this research. However, confidentiality cannot be guaranteed; your personal information may be disclosed if required by law.

To ensure that this research activity is being conducted properly, SUNY Stony Brook's Committee on Research Involving Human Subjects, the Food and Drug Administration, Brookhaven National Laboratory, The National Institute of Health and the Department of

add

Energy have the right to review study and medical records, but confidentiality will be maintained as allowed by law.

IN CASE OF INJURY: If you are injured as a result of being on this study, you should contact Dr. Margaret Kemeny at 631-444-1793. The services of SUNY – Stony Brook's University Hospital and Medical Center will be open to you in case of such injury. However, you or your insurance company will be responsible for payment of any resulting treatment and/or hospitalization.

****

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a copy of this consent form to keep.
- You do not waive any of your legal rights by signing this consent form.

Questions about the Study or Your Rights as a Research Subject

- If you have any questions about the study, you may contact Dr Margaret Kemeny at 631-444-1793.
- If you have any questions about your rights as a research subject, you may contact Dr. Robert Schneider, Committee on Research Involving Human Subjects, 631- 632-9036.

If you sign below, it means that you have read (or have read to you) the information given in this consent form, and you would like to be a volunteer in this study.

_____
Subject Name

_____
Subject Signature Date

_____
Signature of Person Obtaining Consent Date

I willingly agree that a piece of my tissue obtained from my surgery will be used for the research purposes of this study involving PET scanning.

_____
Subject name

_____
Subject Signature Date

_____
Signature of Person Obtaining Consent Date

7/13/00

Subject No: _____

Subject Initials: _____

Item # 8

Brookhaven National Laboratory
Clinical Research Center
Upton, New York 11973

CASE REPORT FORM

IRB Title: **PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960**

Project (IRB) No.: 324

Principal Investigator: _____

Responsible Physician: _____

I have reviewed all the data in the case report forms and found them to be complete and accurate.

_____ _____
Principal Investigator's Signature Date

(To be signed and dated after the subject has ended participation in the study)

Brookhaven National Laboratory

Clinical Research Center

IRB 324

Subject No: _____

Subject Initials: _____

GENERAL INSTRUCTIONS

1. Use black ballpoint ink to record data on these forms.

2. Record the patient's initials (order: first, middle, last) and patient number on the top of each page in the spaces provided. If the patient has no middle initial, please enter a dash (-) or an "X."

3. To make corrections, draw a single line through the error, then record the correct response and initial and date the correction. DO NOT ERASE, OBLITERATE, OR WHITE-OUT ANY ERRORS. Do not make corrections by writing over an erroneous entry.

4. The principal investigator must sign and date the cover page of this case report form after the patient has ended participation in the study.

Brookhaven National Laboratory
Clinical Research Center
IRB 324

Subject No: _____
Subject Initials: _____

MONITORING VISIT LOG

Principal Investigator: _____

DATE	CRA	STUDY CONTACT PERSON

Brookhaven National Laboratory
Clinical Research Center
IRB 324

Subject No: _____
Subject Initials: _____
Visit Date: _____

DEMOGRAPHICS AND PHYSICAL INFORMATION

DEMOGRAPHICS

Date of Birth ___/___/___ (M D Y) Sex ___ M ___ F Race: ___ Caucasian ___ Oriental/Asian ___ Black ___ Hispanic ___ Native American ___ Other _____ specify	If the patient is female, she is: ___ Surgically Sterile _____ specify ___ Post-Menopausal ___ Premenarcheal

VITAL SIGNS

Height:	Weight:	Temperature:	Pulse:	Blood Pressure:
inches	Lbs	°F	bpm	/ mmHg

Brookhaven National Laboratory
Clinical Research Center
IRB 324

Subject No: _____
Subject Initials: _____
Visit Date: _____

SUBJECT ELIGIBILITY CHECKLIST

INCLUSION/EXCLUSION CRITERIA FORM

INCLUSION CRITERIA:		Yes	No	N/A
1.	positive needle biopsy, palpable breast tumor	☐	☐	☐
2.	Ability to understand and give informed consent	☐	☐	☐
3.	>18 years of age	☐	☐	☐

EXCLUSION CRITERIA:				
1.	pregnant	☐	☐	☐
2.	uncontrolled medical disease including diabetes, hepatic or renal disorders, Parkinson's or endocrine disease, psychiatric illness requiring antipsychotic drugs	☐	☐	☐
3.	prior history of radiation and/or chemotherapy	☐	☐	☐
4.	history of anaphylactic reactions	☐	☐	☐
5.	medications which may interfere with COMT activity (for example, tolcapone or other COMT inhibitors)	☐	☐	☐

Brookhaven National Laboratory
Clinical Research Center
IRB 324

Subject No: _____
Subject Initials: _____
Visit Date: _____

BNL Screening and Study Procedures

(Note prescreening examination is carried out at Stony Brook and records are maintained there)

Screening

	Yes	No	NA
1. Lab Consent Form administered (#647)			
2. Study Consent Form administered (#710)			
3. Pregnancy test negative			
4. Drug history completed			
5. PET subject information form completed			
6. Brief physical exam completed			
7. Subject meets eligibility criteria			

Procedure

8. Subject receives [^{18}F]Ro41-0960/PET scan _____ (Y/N)
9. Subject receives cardiac monitoring (HR, BP, EKG (3lead)) _____ (Y/N)
10. Subject receives EKG (12 lead) after PET scan _____ (Y/N)
11. Urine is collected and the counts, volume and time recorded. _____ (Y/N)
12. The subject may be rescanned 1 hour later for 10-20 min. _____ (Y/N)

Date	Run Number	Tracer	Dose	Time

13. Volunteer fee paid _____ (Y/N)
14. Follow-up call next working day by BNL CRC _____ (Y/N)
15. Did subject report an AE or SAE? _____ (Y/N)
    if yes, complete an AE form and state reason below

16. Surgical sample(s) received by BNL (note surgery will occur within 4 weeks of the PET study but samples will not be transferred until a number of samples from different patients have accumulated) _____ (Y/N)

Comments:

_____

_____

_____

Brookhaven National Laboratory

Clinical Research Center

IRB 324

Subject No: _____

Subject Initials: _____

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT.

Date Form Completed: _____

Subject No: _____

Subject Initials: _____

SUBJECT DISPOSITION FORM

Did the subject complete the study?

___ Yes
___ No; state reason for withdrawal below.

Check all that apply:

___ Request of patient
___ Failure to meet eligibility criteria
___ Protocol violation
___ Premenarcheal female begins menses
___ Lost to follow-up/failure to return/moved
___ Pregnancy
___ Adverse event
___ Other (specify details below)*

*Details of withdrawal (if necessary):

_____

_____

_____

_____

_____

_____

_____

Item # 9
CVs

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel listed on the budget page for the initial

NAME	POSITION TITLE
Yu-Shin Ding	Chemist

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
National Taiwan University, Taipei, Taiwan, R.O.C.	B.S.	1979	Chemistry.
SUNY at Stony Brook, Stony Brook, NY	Ph.D.	1987	Org Chem

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1975-1979	Honors, Highest Ranking Scholar, Each Semester, National Taiwan University, Taipei, Taiwan, R.O.C.
1979-1980	Research Assistant, National Taiwan University, Taipei, Taiwan, R.O.C.
1980-1982	Chemistry Teacher, Wesleyan Girl's High School, Taipei, Taiwan, R.O.C.
1982-1984	Graduate Teaching Assistant, SUNY at Stony Brook, Stony Brook, NY
1983-Present	Member, American Chemical Society
1983-1987	Research Assistant, SUNY at Stony Brook, Stony Brook, NY
1987-1990	Post Doc, Chemistry Dept., Brookhaven National Laboratory, Upton, NY
1988-Present	Member, Society of Nuclear Medicine
1990-1992	Assistant Chemist, Chemistry Dept., Brookhaven National Laboratory, Upton, NY
1992-1994	Associate Chemist, Chemistry Dept., Brookhaven National Laboratory, Upton, NY
1992-Present	Member, Review Committee for Society of Nuclear Medicine Annual Meeting
1994-Present	Chemist, Chemistry Dept., Brookhaven National Laboratory, Upton, NY
1993-Present	Member, Scientific Program Committee, Society Nuclear Medicine Annual Meeting
1996	Member, Grant Review Committee of National Institute on Aging, Ad-hoc Program Project Review Committee, Albin Site Visit, Ann Arbor, Michigan (May 13-14)
1997	Member, Grant Review Committee of National Institute on Aging, Program Project Review Committee, Teleconference, Ann Arbor, Michigan (March 26)
1996	Sub-Chair, Positron Category of Radiopharmaceutical Chemistry, Society of Nuclear Medicine, Annual Meeting
1996-2001	First Independent Research Support and Transition Award (FIRST-R29), "PET Studies of Catechol-O-Methyltransferase" National Institutes of Health NIH/NINDS
1997-Present	Member, Board of Directors, Radiopharmaceutical Science Council, Society of Nuclear Medicine

Journal Referee:

Journal of Labeled Compounds and Radiopharmaceuticals; Journal of Pharmacology and Experimental Therapeutics; Journal of Medicinal Chemistry; Journal of Nuclear Medicine; Nuclear Medicine and Biology; Life Sciences

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Ding Y-S, Shiue C-Y, Fowler JS, Wolf AP, and Plenevaux A: No-Carrier-Added (NCA) Aryl[^{18}F]Fluorides Via the Nucleophilic Aromatic Substitution of Electron Rich Aromatic Rings. J. Fluorine Chem., 48:189-205 (1990).

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Ding Y-S, Fowler JS, Dewey SL, Logan J, Schlyer D, Gatley SJ, Volkow ND, King P, and Wolf AP: Comparison of High Specific Activity 6-[^{18}F]-Fluorodopamine and (+) and (-)-6-[^{18}F]Fluoronorepinephrine in Baboon; Heart Uptake, Metabolism and the Effect of Desipramine. J. Nucl. Med., 34:619 (1993).

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Volkow ND, Ding Y-S, Fowler JS, Wang G-J, Logan J, Gatley SJ, Dewey S, Ashby C, Liebermann J, Hitzemann R, and Wolf AP: Is Methylphenidate Like Cocaine? Studies on Their Pharmacokinetics and Distribution in Human Brain. Arch. Gen. Psychiatry, 52: 456-463 (1995).

Ding Y-S, Fowler JS, Volkow ND, Logan J, Gatley SJ, and Sugano Y: Carbon-11-*d-threo*-Methylphenidate Binding to Dopamine Transporter in Baboon Brain. J. Nucl. Med., 36: 2298-2305 (1995).

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Ding Y-S, Gatley SJ, Fowler JS, Volkow ND, Aggarwal D, Logan J, Dewey SL, Liang F, Carroll FI, Kuhar MJ: Mapping Nicotinic Acetylcholine Receptors with PET. Synapse, 24:403-407, (1996).

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

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Gatley SJ, Ding Y-S, Brady D, Volkow ND, Gifford AN, Dewey SL, Carroll FI, Fowler JS, Volkow ND: In vivo and Ex vivo Autoradiographic Studies of Nicotinic Acetylcholine Receptors Using [^{18}F]Fluoro-norchloroepibatidine in Rodent and Human Brain. Nucl. Med. Biol. (in press, 1998).

Molina PE, Ding Y-S, Carroll FI, Liang F, Volkow ND, Pappas N, Kuhar M, Abumrad N, Gatley SJ, Fowler JS: Fluoronorchloroepibatidine-Preclinical assessment of acute toxicity. Nucl. Med. Biol 24, 743-747, (1997).

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Ding Y-S, Molina PE, Fowler JS, Logan JS, Volkow ND, Kuhar MJ and Carroll FI: Comparative Studies of Epibatidine Derivatives [^{18}F]NFEP and [^{18}F]N-Methyl-NFEP: Kinetics, Nicotine Effect and Toxicity. Nucl. Med.Biol., (submitted, 1998).

Ding Y-S, Logan JS, Gatley SJ, Fowler JS, Volkow ND: PET Studies of Peripheral Catechol-O-methyltransferase in Non-human Primates Using [^{18}F]Ro41-0960. J. Neural. Transm., (submitted, 1998).

Fowler JS, Volkow ND, Ding Y-S and Wang G-J. Positron Emission Tomography (PET) and the Study of Drug Action in the Human Brain. Pharmaceutical News, (in press, 1998).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel listed on the budget page for the initial budget period

NAME	POSITION TITLE
Joanna S. Fowler	Senior Chemist

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
University of South Florida, Tampa, FL	B.A.	1964	Chemistry
University of Colorado, Boulder, CO	Ph.D.	1967	Chemistry
University of East Anglia, England	Post-Doc.	1968	Org. Chem.
Brookhaven National Laboratory, Upton NY	Post-Doc.	1969-70	Org. Synth.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1971-1982	Chemist, Chemistry Dept., Brookhaven National Laboratory, Upton, NY
1980-1992	Editorial Board, Journal of Nuclear Medicine
1986-1992	NCR Committee on Nuclear and Radiochemistry
1986-1988	Member, Board of Directors, Radiopharmaceutical Science Council, Society of Nuclear Medicine
1987-1991	NIH, Diagnostic Radiology Study Section
1983-	Tenured Chemist, Chem. Dept., Brookhaven National Laboratory, Upton, NY
1986	The Javits Neuroscience Investigator Award, as Co-P.I. (jointly with A. P. Wolf)
1988	ACS N.E. Section Esselen Award for Chemistry in the Public Interest
1990	US Pharmacopeia Advisory Board
1990-1992	Editorial Board, Synapse
1990-1993	Scientific Program Committee, Society of Nuclear Medicine
1990-Present	Member, Advisory Panel on Radiopharmaceuticals Appointed by the United States Pharmacopeial Convention, Inc. (USP)
1991	Brookhaven Town, Office of Women's Services, National Women's History Month
1993-	Member ,Advisory Committee for Imaging Center, Yale University, New Haven, CT
1994-	The Javits Neuroscience Investigator Award (awarded for seven years)
1994-Present	Director, Cyclotron-PET Program, Brookhaven National Laboratory, Upton, NY
1994-Present	Member, Board of Chemical Sciences and Technology
1994-Present	Member, TRIUMF, Life Sciences Visiting Committee
1995-Present	Member, Board of Scientific Councelors, National Institute on Drug Abuse
1996-Present	Member, Board of Directors, Society for Nuclear Imaging in Drug Research
1997	BER 50 Program Recognition Award for Exceptional Service (Department of Energy and National Research Council), Washington, DC
1997	Paul C. Aebersold Award, Society of Nuclear Medicine, San Antonio, Texas
1998	Francis P. Garvan-John M. Olin Medal, ACS National Meeting, Dallas, Texas

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Yousef KA, Fowler JS, Volkow ND, Dewey SL, Shea C, Schlyer DJ, Gatley SJ, Logan J and Wolf AP: [^{18}F]Haloperidol Binding in Baboon Brain In Vivo. Nucl. Med. Biol. 23, 47-52 (1996).

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Gatley SJ, Volkow ND, Chen R, Fowler JS, Carroll FI and Kuhar MJ: Displacement of RTI-55 from the Dopamine Transporter of Cocaine. Eur. J. Pharmacology 296, 145-151 (1996).

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Volkow ND, Fowler JS, Gatley SJ, Logan J, Wang G-J, Ding Y-S and Dewey S: PET Evaluation of the Dopamine System of the Human Brain. J. Nucl. Med. 37(7), 1242-1256 (1996).

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Wang GJ, Volkow ND, Fowler JS, Logan J, Gur R, Netusil N, Hitzemann RJ and Pappas NS: Age Associated Decrements in Dopamine D2 Receptors in Thalamus and in Temporal Insula of Human Subjects. Life Sci. 59(1), PL 31-35 (1996).

Wang GJ, Volkow ND, Levy AV, Fowler JS, Logan J, Alexoff D, Hitzemann R and Schlyer DJ: MR-PET Image Coregistration for Quantitation of Striatal Dopamine D2 Receptors. J. Comp. Assist. Tomography 20(3), 423-428 (1996).

Volkow ND, Gatley SJ, Fowler JS, Logan J, Fischman M, Gifford AN, Pappas N, King P, Vitkun S, Ding Y-S and Wang G-J: Cocaine Doses Equivalent to Those Abused by Humans Occupy Most of the Dopamine Transporters. Synapse 24, 399-402 (1996).

Wang G-J, Volkow ND, Lau YH, Fowler JS, Meek AG, Park TL, Wong C, Roque CT, Adler AJ and Wolf AP: Glucose Metabolic Changes in Nontumoral Brain Tissue of Patients with Brain Tumor Following Radiotherapy: A Preliminary Study. J. Comp. Assist. Tomography 20, 709-714 (1996).

Volkow ND, Wang G-J, Fowler JS, Logan J, Hitzemann R, Ding Y-S, Pappas N, Shea C and Piscani K: Decreases in Dopamine Receptors But Not in Dopamine Transporters in Alcoholics. Alcohol. Clin. Exp. Res. 20, 1594-1598 (1996).

Fowler JS and Wolf AP: Working Against Time: Rapid Radiotracer Synthesis and Imaging the Human Brain. Accts. Chem. Res. 30, 181-188 (1997).

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Wang G-J, Volkow ND, Overall J, Hitzemann RJ, Pappas N, Pascani K and Fowler JS: Reproducibility of Regional Brain Metabolic Responses to Lorazepam. J. Nucl. Med. 37, 1609-13 (1996).

Ding Y-S, Fowler JS, Volkow ND, Dewey SL, Wang G-J, Gatley J, Logan J and Pappas N: Chiral Drugs: Comparison of the Pharmacokinetics of [^{11}C]*d-threo* and *l-threo*-Methylphenidate in the Human and Baboon Brain. Psychopharmacology 131, 71-78 (1997).

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Fowler JS, Volkow ND, Wang G-J, Logan J, Pappas N, Shea C and MacGregor R: Age-Related Increases in Brain MAO B in Healthy Human Subjects. Neurobiol. Aging 18(4), 431-435 (1997).

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Logan J, Volkow ND, Fowler JS, Wang G-J, Fischman MW, Foltin RW, Abumrad NN, Vitkun S, Gatley SJ, Pappas N, Hitzemann R and Shea CE: Concentration and Occupancy of Dopamine Transporters in Cocaine Abusers with [^{11}C]-Cocaine and PET. Synapse 27, 347-356 (1997).

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Ding Y-S, Liang F, Fowler JS, Kuhar MJ and Carroll FI: Synthesis of [^{18}F]Norchlorofluoro-epibatidine and Its N-Methyl Derivative: New PET Ligands for Mapping Nicotinic Acetylcholine Receptors. J. Label. Cmpds. Radiopharm. 39(10), 827-832 (1997).

Wang G-J, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann R, Pappas N and Pascani K: Dopamine D2 Receptor Availability in Opiate-Dependent Subjects Before and After Naloxone-Precipitated Withdrawal. Neuropsychopharmacology 16, 174-182 (1997).

Molina PE, Ding Y-S, Carroll FI, Liang F, Volkow ND, Pappas N, Kuhar M, Abumrad N, Gatley SJ and Fowler JS: Fluoro-norchloroepibatidine: Preclinical Assessment of Acute Toxicity. Nucl. Med. Biol. 24, 743-747 (1997).

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Volkow ND, Gur RC, Wang G-J, Fowler JS, Moberg P, Ding Y-S, Logan J and Smith G: Association Between Decline in Brain Dopamine Activity with Age and Cognitive and Motor Impairment in Healthy Individuals. Am. J. Psychiatry 155(3), 344-340 (1998).

Fowler JS, Volkow ND, Logan J, Gatley SJ, Pappas N, King P, Ding Y-S and Wang G-J: Measuring Dopamine Transporter Occupancy by Cocaine *In Vivo*: Radiotracer Considerations. Synapse 28, 111-116 (1998).

Volkow ND, Wang G-J, Fowler JS, Hitzemann R, Gatley SJ, Dewey SL, and Pappas N: Enhanced Sensitivity to Benzodiazepines in Cocaine Abusers: A PET Study. Am. J. Psychiatry 155(2), 200-206 (1998).

Volkow ND, Wang GJ, Fowler JS, Ding Y-S, Gur RC, Gatley J, Logan J, Moberg PJ, Hitzemann R, Smith G and Pappas N: Parallel Loss of Pre and Postsynaptic Dopamine Markers in Normal Aging. Ann Neurology (in press).

Fowler JS, Volkow ND, Logan J, Pappas N, King P, MacGregor R, Shea C, Garza V, and Gatley SJ: An Acute Dose of Nicotine Does Not Inhibit MAO B in Baboon Brain In Vivo. Pharmacology Letters (in press).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel listed on the budget page for the initial budget period

NAME	POSITION TITLE
Nora D. Volkow	Scientist

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Modern American School, Mexico City	B.A.	1974	Biomedicine
National University Mexico	M.D.	1981	Medicine
New York University	Residency	1984	Psychiatry

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1975-1976	Research Assistant, Electron Microscopy, Dept. Pathology, Registro National de Anatomia Patologica, Mexico City
1977-1978	Research Assistant, Miles Lab. Exp. Therap., Mexico City, Mexico
1979-1980	Intern, Centre des Maladies et de l'Encephale, Sainte Anne Psychiatric Hospital, Paris, France
1981-1984	Resident Deparmtent of Psychiatry, New York University, New York, NY
1981-1987	Research Collaborator, Chemistry Department, Brookhaven National Laboratory Upton, NY
1984-1987	Assistant Professor, Department of Psychiatry and Behavioral Science, University of Texas Medical School
1987-1990	Associate Scientist, Brookhaven National Laboratory, Upton, NY
1987-1990	Assistant Professor, Department of Psychiatry, SUNY Stony Brook, NY
1989-present	Scientist, Brookhaven National Laboratory, Upton, New York
1991-present	Associate Professor, Department of Psychiatry, SUNY Stony Brook, NY
1994-present	Director Nuclear Medicine, Medical Department Brookhaven National Laboratory, Upton, NY
1996-present	Chairman, Medical Department, Brookhaven National Laboratory, Upton, NY
1998-present	Associate Dean, School of Medicine SUNY/Stony Brook at Brookhaven National Laboratory, Upton, NY

Honors

1978	Premio Robins - Best Medical Student of the Generation,U.N.A.M.
1981	National Award for the Outstanding Medical Student
1981	Premio Gabino Barrera - Best Student National University of Mexico (U.N.A.M.)
1984	Laughlin Fellowship Award
1985	Scanditronix Scholarship
1995	Distinguished Research and Development Award, Brookhaven National Laboratory
1998	Brookhaven Town, Office of women's Services, National Women's History Month

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

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Volkow ND, Fowler JS, Wolf AP, Hitzemann R, Dewey S, Bendriem B, Alpert R and Hoff A. Changes in Brain Glucose Metabolism in Cocaine Dependence and Withdrawal. Am J Psychiatry, 148, 621-626 (1991).

Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue C-Y, Dewey SL, Alpert R, Logan J, Christman D, Bendriem B, Hitzemann R and Henn F. Effects of Chronic Cocaine Abuse on Postsynaptic Dopamine Receptors. Am J Psychiatry, 147, 719-724 (1990).

Volkow ND, Hitzemann R, Wang G-J, Fowler JS, Burr G, Piscani K, Dewey SL and Wolf AP. Decreased Brain Metabolism in Neurologically Intact Healthy Alcoholics. Am J Psychiatry, 149, 1016-1022 (1992).

Volkow ND, Wang G-J, Hitzemann R, Fowler JS, Wolf AP, Pappas N, Biegon A and Dewey SL. Decreased Cerebral Response to Inhibitory Neurotransmission in Alcoholics. Am J Psychiatry, 150, 417-422 (1993).

Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer DJ, Dewey SL and Wolf AP. Decreased Dopamine D_2 Receptor Availability Is Associated With Reduced Frontal Metabolism in Cocaine Abusers. Synapse, 14, 169-177 (1993).

Volkow ND, Wang G-J, Hitzemann R, Fowler JS, Burr G and Wolf AP. Recovery of Brain Glucose Metabolism in Detoxified Alcoholics. Am J Psychiatry, 151, 178-183 (1994).

Volkow ND, Fowler JS, Wang G-J, Logan J, Schlyer D, MacGregor R, Hitzemann R and Wolf AP. Decreased Dopamine Transporters with Age in Healthy Human Subjects. Annals of Neurology, 36, 237-239 (1994).

Volkow ND, Ding Y-S, Fowler JS, Wang G-J, Logan J, Gatley SJ, Dewey S, Ashby C, Liebermann J, Hitzemann R and Wolf AP. Is Methylphenidate Like Cocaine? Studies on Their Pharmacokinetics and Distribution in Human Brain. Arch. Gen. Psychiatry, 52, 456-463 (1995).

Volkow ND, Ding Y-S, Fowler JS, Wang G-J, Logan J, Gatley SJ, Schlyer DJ and Pappas N. A New PET Ligand for the Dopamine Transporter: Studies in the Human Brain. J. Nucl. Med., 36, 2162-2168 (1995).

Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, MacGregor RR, Schlyer DJ, Hitzemann R and Wolf AP. Measuring Age Related Changes in Dopamine D_2 Receptors with [^{11}C]Raclopride and [^{18}F]N-Methylspiroperidol. Psychiatry Res., 67, 11-16 (1996).

Volkow ND, Wang G-J, Hitzemann R, Fowler JS, Pappas N, Lowrimore P, Burr G, Pascani K, Overall J and Wolf AP. Depression of Thalamic Metabolism by Lorazepam is Associated with Sleepiness. Neuropsychopharmacology, 12(2), 123-132 (1995).

Volkow ND, Ding Y-S, Fowler JS, Wang G-J, Logan J, Gatley SJ, Hitzemann R, Smith G, Fields SD and Gur R. Dopamine Transporters Decrease with Age. J. Nucl. Med., 37(4), 554-559 (1996).

Volkow ND, Fowler JS, Gatley SJ, Logan J, Wang G-J, Ding Y-S and Dewey S. PET Evaluation of the Dopamine System of the Human Brain. J. Nucl. Med., 37(7), 1242-1256 (1996).

Wang GJ, Volkow ND, Lau YH, Fowler JS, Meek AG, Parl TL, Wong C, Rocque CT, Adler AJ, Wolf AP. Glucose metabolic changes in nontumoral brain tissue of patients with brain tumor following radiotherapy: a preliminary study. J Comp Assisted Tomography 20: 709-714 (1996).

Ding Y-S, Gatley SJ, Fowler JS, Volkow ND, Aggarwal D, Logan J, Dewey S, Liang F, Carroll FI, Kuhar MJ. Mapping nicotinic acetylcholine receptors with PET. Synapse 24:403-407 (1996).

Volkow ND, Wang G-J, Fowler JS, Gatley SJ, Ding Y-S, Logan J, Dewey SL, Hitzemann R, Lieberman J. Relationship between psychostimulant induced high and dopamine transporter occupancy. Proceedings National Academy of Sciences 93: 10388-10392 (1996).

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

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Ding Y-S D, Fowler JS, Volkow ND, Dewey SL, Wang G-J, Gatley J, Logan J, Pappas, N. Chiral drugs: comparison of the pharmacokinetics of [11C]d-threo and l-threo methylphenidate in the human and baboon brain. Psychopharmacology 131:71-78, (1997).

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Wang G-J, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann RJ, Pappas NS, Pascani K. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone precipitated withdrawal. Neuropsychopharmacology 16:174-182 (1997).

Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea K. Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386:827-830 (1997).

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Wang G-J, Volkow ND, Fowler JS, Fischman MW, Foltin RW, Abumrad NN, Logan J, Pappas N. Cocaine abusers do not show age-related losses of dopamine transporters. Life Sciences 61: 1059-1065 (1997).

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel listed on the budget page for the initial budget period

NAME	POSITION TITLE
Gene-Jack Wang	Scientist

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include post-doctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY
Kaohsiung Medical College, Kaohsiung, Taiwan	M.D.	1980	Medicine
Master of Health Sciences (Radiation Hlth. Sci.) Johns Hopkins University, Baltimore, MD	M.H.S.	1982-1984	Radiation

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and to representative earlier publications pertinent to this application. If the list of publications in the last 3 years exceeds 2 pages, select the most pertinent publications. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

1979 - 1980	Rotation Intern, Kaohsiung Medical College Hospital, Kaohsiung, Taiwan
1980 - 1982	Medical Officer, Army Clinics, Taipei, Taiwan
1983 - 1984	Research Assistant, Division of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, MD
1984 - 1986	Resident in Nuclear Medicine, University of Missouri at Columbia Hospital and HSTMV Hospital, Columbia, Missouri
1986 - 1988	Fellow in Hematology, Albany Medical College & Albany Veterans Administration Hospital, Albany, NY
1988 - 1990	Clinical Assistant Instructor in Nuclear Radiology, State University of New York at Stony Brook, Stony Brook, New York
1988 - 1990	Fellow in Nuclear Radiology, State University of New York Health Sciences Center at Stony Brook, Stony Brook, NY
1988 - 1990	Research Collaborator, Medical Department, Brookhaven National Laboratory, Upton, NY
1990 - 1992	Assistant Scientist, Medical Dept., Brookhaven National Laboratory, Upton, NY
1992 - 1995	Associate Scientist, Medical Dept., Brookhaven National Laboratory, Upton, NY
1992 - Present	Assistant Professor of Radiology, SUNY Stony Brook, Stony Brook, NY
1995 - Present	Scientist, Medical Department, Brookhaven National Laboratory, Upton, NY
1996 - 1998	Associate Chief of Staff, Clinical Research Center, Medical Department, Brookhaven National Laboratory, Upton, New York
1996 - Present	Clinical Head of PET and SPECT Facilities and Clinical Research Center, Medical Department, Brookhaven National Laboratory, Upton, NY
1998 - Present	Chief of Staff, Medical Dept., Brookhaven National Laboratory, Upton, NY

License and Certification: 1982 ECFMG #347 - 188 - 5; 1986 Missouri State License #36820 (inactive); 1989 New York State License #179469; 1989 American Board of Nuclear Medicine #05316

Membership of Medical Society: 1985 - Society of Nuclear Medicine; 1986 - American College of Nuclear Physicians; 1988 - The Radiological Society of North America; 1989 - American Medical Association; 1989 - Chinese American Society of Nuclear Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Wang G-J, Volkow ND, Hitzemann RJ, Pappas NR, Pascarni K, Fowler JS: Reproducibility of Regional Brain Metabolic Responses to Lorazepam. J Nucl Med; 1996; 37(10):1609-1613.

Volkow ND, Ding Y-S, Fowler JS, Wang G-J: Cocaine Addiction: Hypothesis Derivated from Imaging with PET. J Addic Disease; 1996; 15(4):55-71.

Volkow ND, Gatley SJ, Fowler JS, Logan J, Fischman M, Gifford AN, Pappas NR, King P, Vitkun S, Ding Y-S, Wang G-J: Cocaine Doses Equivalent to Those Abused by Humans Occupy Most of The Dopamine Transporters. Synapse; 1996; 24:399-402.

Volkow ND, Wang G-J, Fowler JS, Gatley SJ, Ding Y-S, Logan J, Dewey SL, Hitzemann RJ, Lieberman J. Relationship between Psychostimulant-Induced High and Dopamine Transporter Occupancy. Proc Natl Acad Sci 1996; 93(19): 10388-10392.

Volkow ND, Wang G-J, Fowler JS, Logan J, Hitzemann RJ, Ding Y-S, Pappas NR, Shea CE, Pascani K. Decreases in Dopamine Receptors but not in Dopamine Transporters in Alcoholics. Alcohol Clin Exper Res; 1996; 20(9):1594-1598.

Fowler JS, Volkow ND, Wang G-J, Pappas NR, Logan J, Shea CE, Alexoff DL, MacGregor RR, Schlyer DJ, Zelzukova I, Wolf AP: Brain Monoamine Oxidase A Inhibition in Cigarette Smokers Proc Natl Acad Sci 1996; 93:14065-14069.

Volkow ND, Wang G-J, Fowler JS, Logan J, Hitzemann RJ, Lieberman J, Pappas NR. Effects Of Methylphenidate on Regional Brain Glucose Metabolism in Humans: Relationship to Dopamine D_2 Receptors. Amer J Psychiatry; 1997; 154(1):50-55.

Gatley SJ, Volkow ND, Gifford AN, Ding Y-S, Logan J, Wang G-J: Model for Estimating Dopamine Transporter Occupancy and Subsequent Increases in Synaptic Dopamine Using Positron Emission Tomography and Carbon-11 Labeled Cocaine. Biomed Pharmacology; 1997; 53:43-52.

Wang G-J, Volkow ND, Fowler JS, Logan J, Abumred NN, Hitzemann RJ, Pappas NR, Pascani K: Dopamine D_2 Receptors Availability in Opiate-Dependent Subjects before and after Naloxone-Precipitated Withdrawal. Neuropsychopharmacology; 1997; 16:174-182.

Wang G-J, Volkow ND, Wong CT, Hitzemann RJ, Fowler JS, Angrist B, Burr G, Pascarni K, Pappas NR, Lu A, Cooper J, Lieberman J: Behavior and Cardiovascular Effects of Intravenous Methylphenidate in Normal Subjects and Cocaine Abusers. Eur Addic Res; 1997; 3:49-54.

Volkow ND, Wang G-J, Fowler JS, Hitzemann RJ, Pappas NR, Pascarni K, Wong CT: Gender Differences in Cerebellar Metabolism: Test-Retest Reproducibility. Amer J Psychiatry; 1997; 154(1):119-121.

Volkow ND, Wang G-J, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas NR, Hitzemann RJ, Shea CE: Relationship between Subjective Effects of Cocaine and Dopamine Transporter Occupancy. Nature; 1997; 386:827-830.

Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Hitzemann RJ, Chen AD, Dewey SL, Pappas NR: Decreased Striatal Dopaminergic Responsiveness in Detoxified Cocaine-Dependent Subjects. Nature; 1997; 386:830-833.

Ding Y-S, Fowler JS, Volkow ND, Dewey SL, Wang G-J, Logan J, Gatley SJ, Pappas NR: Chiral Drugs: Comparison of the Pharmacokinetics of [C-11]*d-threo* and *l-threo*-Methylphenidate in the Human and Baboon Brain. Psychopharmacology; 1997; 131(1):71-78.

Wang G-J, Volkow ND, Fowler JS, Fischman MW, Foltin RW, Abumrad NN, Logan J, Pappas NR, Hitzemann RJ, Shea CE: Cocaine Abusers do not Show Age-Related Losses of Dopamine Transporters. Life Sciences 1997; 61(11): 1059-1065.

Logan J, Volkow ND, Fowler JS, Wang G-J, Fischman MW, Foltin RW, Abumrad NN, Vitkun S, Gatley SJ, Pappas NR, Hitzemann RJ, Shea CE: Concentration and Occupancy of Dopamine Transporters in Cocaine Abusers with [C-11]cocaine and PET. Synapse 1997; 27(4): 347-356.

Volkow ND, Wang G-J, Fowler JS, Hitzemann RJ, Gatley SJ, Dewey SL, Pappas NR: Enhanced Sensitivity to Benzodiazepines in Cocaine Abusers: A PET Study. Amer J Psychiatry 1998; 155(2): 200-206.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Fowler JS, Volkow ND, Logan J, Gatley SJ, Pappas NR, King P, Ding Y-S, Wang G-J: Measuring Dopamine Transporter Occupancy by Cocaine in vivo: Radiotracer Considerations. Synapse 1998; 28(2): 111-116.

Volkow ND, Gur RC, Wang G-J, Fowler JS, Moberg PJ, Ding Y-S, Hitzemann RJ, Smith G, Logan J: Association Between Decline in Brain Dopamine Activity with Age and Cognitive and Motor Impairment in Healthy Individuals . Amer J Psychiatry 1998; 155(3): 344-349.

Fowler JS, Volkow ND, Wang G-J, Pappas NR, Logan J, MacGregor RR, Alexoff DL, Wolf AP, Warner D, Cilento R, Zezulkova I: Neuropharmacological Actions of Cigarette Smoke: Brain Monoamine Oxidase B (MAOB) Inhibition. J Addictive Disease; 1998; 17 (1): 23-34.

Wang G-J, Volkow ND, Hitzemann RJ, Pappas NR, Pascarni K, Fowler JS: Evaluation of Gender Difference in Regional Brain Metabolic Responses to Lorazepam. Psychiatry Research: Neuroimaging; In press.

Volkow ND, Wang G-J, Fowler JS, Ding Y-S, Gur RC, Gatley SJ, Logan J, Moberg PJ, Smith G, Pappas NR: Parallel Loss of Pre and Postsynaptic Dopamine Markers in Normal Aging. Arch Gen Psychiatry; In press.

Volkow ND, Wang G-J, Fowler JS, Gatley SJ, Logan J, Ding Y-S, Pappas NR: Therapeutic Doses of Oral Methylphenidate Induce Low Levels of Dopamine Transporter Occupancy and Have a Slow Rate of Brain Uptake: Implications for its Reinforcing Effects. J Amer Med Assoc (Submitted).

Volkow ND, Fowler JS, Wang G-J, Gatley SJ, Ding Y-S: Pharmacological Imaging with Positron Emission Tomography: Drugs of Abuse. Proc Natl Acad Sci (Submitted).

Wang G-J, Volkow ND, Levy A, Felder CA, Fowler JS, Pappas NR, Hitzemann RJ, Wong CT: Measuring Reproducibility of Regional Brain Metabolic Responses to Lorazepam Using Statistical Parametric Maps (SPM). J Nucl Med; (Submitted).

Wang G-J, Volkow ND, Fowler JS, Pappas NR, Wong CT, Felder CA, Hitzemann RJ: Regional Cerebral Metabolism in Female Alcoholics of Moderate Severity Does Not Differ from That of Controls. Alcoholism: Clinical and Experimental Research; (Submitted).

Volkow ND, Wang G-J, Fowler JS, Gatley SJ, Ding Y-S: Dopamine Transporter Occupancies After Therapeutic Doses of Oral Methylphenidate: Implications for its Abuse Liability. New Engl J Med (Submitted).

Volkow ND, Wang G-J, Fowler JS, Hitzemann RJ, Angrist B, Gatley SJ, Ding Y-S, Pappas NR: Activation Of Striato-Orbitofrontal Metabolism By Methylphenidate In Cocaine Abusers Is Associated With Drug Craving: Implications In Drug Addiction. Science (Submitted).

Volkow ND, Wang G-J, Fowler JS, Hitzemann RJ, Gatley SJ, Angrist B, Ding Y-S, Wong CT, Pappas NR: Differences In Regional Brain Metabolic Responses To Single Than To Repeated Doses Of Methylphenidate. Amer J Psychiatry (Submitted).

Volkow ND, Fowler JS, Gatley SJ, Dewey SL, Wang G-J, Logan J, Ding Y-S, Franceschi D, Gifford A, Morgan A, Pappas NR, King P: Comparable Changes In Synaptic Dopamine Induced By Methylphenidate And By Cocaine In The Baboon Brain. Amer J Psychiatry (Submitted).

Wang G-J, Volkow ND, Fowler JS, Logan J, Pappas NR, Natusil N, Wong CT, Hitzemann RJ: Reproducibility Of Repeated Measures Of Endogenous Dopamine Competition With [C-11]raclopride In The Human Brain. J Nucl Med; (Submitted).

Volkow ND, Fowler JS, Gatley SJ, Logan J, Wang G-J, Ding Y-S, Dewey SL: PET Evaluation of the Dopamine System of the Human Brain . J Nucl Med 1996; 37(7):1242-1256.

Volkow ND, Wang G-J, Fowler JS: Imaging Studies of Cocaine in the human brain and studies of the Cocaine Addict. Annals of New York Academy of Sciences 1997; 820:41-54.

Volkow ND, Fowler JS, Wang G-J, Logan J: Measuring Dopamine Release in the Human Brain with PET. The Bio-Clinical Interface. Macher J-P, Crocq M-A, Nedelec J-F, eds. France 1997; 355-361.

Volkow ND, Fowler JS, Ding Y-S, Wang G-J, Gatley SJ: PET Radioligands for Dopamine Transporters and Studies in Human and Nonhuman Primates. Advances in Pharmacology 1998; 42: 211-214.

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SUMMARY

Registered nurse with over 7 years of experience in clinical research. Experience includes enrollment of subjects, study visits, data collection, maintainence of regulatory documents, contact with institutional IRB, consenting procedures, accountability of test article, adverse event reporting, laboratory testing/specimen collection and follow up, extensive subject recruitment/screening, and completion of case report forms.

EXPERIENCE

5/00 to present	**Clinical Research Coordinator** Medical Department Brookhaven National Laboratory, Upton, NY
10/98 to 5/00	**Research Coordinator** Department of Infectious Diseases. University Hospital State University of New York at Stony Brook, Stony Brook, NY
1995 - 03/98	**Community Health Nurse, Long Term Home Health Care & AIDS Program** Brookhaven Memorial Hospital and Medical Center Home Care, Patchogue, NY
1994 – 1995	**IV Therapy Nurse Clinician** Vital Home Care, Inc. Farmingdale, NY
1993 - 1994	**IV Therapy Nurse Clinician** Critical Care America, Totowa, NJ
1987 - 1992	**AIDS Research Coordinator/Medical Oncology** St Vincent's Hospital and Medical Center of New York, NY
1985 - 1987	**Staff Nurse**, Coronary Intensive Care

EDUCATION

Jan 2000	Dowling College, NY **MBA**
May 1980	State University of New York at Farmingdale **A.S. Nursing**
May 1978	State University of New York at Stony Brook **B.A. Psychology**

CREDENTIALS/LICENSURE

1997	Certification in HIV/AIDS nursing
1980	Registered Professional Nurse, New York #329539

PROFESSIONAL MEMBERSHIP

1997	Appointed, Suffolk County, NY HIV Commission
1990-1992	Board of Directors , Association of Nurses in AIDS Care
1989	Founding member & First President, Association of Nurses in AIDS Care, Greater NY Chapter
1987	President, not for profit religious corporation.

PII Redacted

Mary Margaret Kemeny, M.D., F.A.C.S.

PERSONAL

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HSC T-18, Room 60
Stony Brook, NY 11794-8191

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E-mail: kemeny@surg.som.sunysb.edu

CURRENT POSITION

Chief, Division of Surgical Oncology
SUNY Stony Brook
Stony Brook, NY 11794-8191

Professor of Surgery
State University of New at Stony Brook
(Appointment Pending)

BOARD CERTIFICATION

1983 Diplomate of American Board of Surgery
1986 Fellow, American College of Surgeons
1993 Recertification American Board of Surgery

MEMBERSHIPS

Commission on Cancer
American Society of Clinical Oncology
Society of Surgical Oncology
American Association of Immunologists
New York Cancer Society
New York Surgical Society
Board of Directors, American Cancer Society(Manhattan Division)
Association of Women Surgeon
American Association for Cancer Research

EDUCATION

High School	Vail-Deane School
College	Harvard College 1968 - B.S. Degree, Cum Laude
Medical School	Columbia University College of Physicians and Surgeons 1972 - M.D. Degree

INTERNSHIP AND RESIDENCY

1972 - 1974	Presbyterian Hospital, New York
1974 - 1975	University of Colorado Medical Center
1977 - 1979	Senior Year Surgical Residency and Chief Residency Downstate Medical Center

FELLOWSHIP

1975 - 1976	Fellowship in Tumor Oncology Memorial Sloan-Kettering Cancer Center
1976 - 1977	Research Fellowship in Thoracic Surgery Memorial Sloan-Kettering Cancer Center
1979 - 1981	Clinical Associate of Surgical Branch National Cancer Institute, NIH Bethesda, Maryland

POSITIONS

1981 - 1986	Senior Surgeon, General and Oncologic Surgery City of Hope National Medical Center 1500 East Duarte Road Duarte, California 91010
1986 - 1993	Chief, Surgical Oncology St. Vincent's Hospital and Medical Center New York, NY 10011
	Associate Professor of Surgery New York Medical College

1993 - 1998	Chief, Division of Surgical Oncology North Shore University Hospital-NYU Manhasset, New York 11030

AWARDS AND APPOINTED POSITIONS

Present- 1990	Member of Leadership Council Association of Women Surgeons
Present - 1991	Head of the Committee on Issues Association of Women Surgeons
1997	Member of the Task Force Committee on Research on Women's Health for the 21st Century, Office of Research on Women's Health, NIH.
2001 -1991	Member of the Commission on Cancer, American College of Surgeons.
2001 - 1991	Member of the Medical Devices Advisory Committee, Center for Devices and Radiological Health Food and Drug Administration.
1998	Faculty Member of ASCO/AACR Workshop entitled "Methods in Clincal Cancer Research
1997- 1996	President, Association of Women Surgeons
1997 -1994	Chair, Committee on Approvals, Commission on Cancer, American College of Surgeons
1997 - 1994	Executive Committee, Commission on Cancer, ACS
1997 - 1996	Member of the Special Ad Hoc Working Group on the Women's Health Initiative Advisory Committee on Reasearch on Women's Health, NIH
1997 - 1993	Member of the Examination Committee for the Society of Surgical Oncology, Inc.
1997-	Editor, American Journal of Surgery
1997	Member of GI Program Committee, ASCO
1997	Chair GI Slide Session, ASCO Annual Meeting, Denver, Colorado.
1997	Faculty Member of ASCO/AACR Workshop entitled "Methods in Clincal Cancer Research"

	Medical Grand Rounds St. Vincent's Hospital and Medical Center
5/23/89	Role of Splenectomy for Thrombocytopenia in AIDS and HIV Seropositive Patients. American Society Clinical Oncology (ASCO) Annual Meeting Poster
6/7/89	Randomized Studies of Hepatic Arterial Infusion of FUDR in Patients with Liver Metastases from Colon Cancer IV. Internation Conference on Advances in Regional Chemotherapy Berchtesgaden, West Germany
6/8/89	Surgical Grand Rounds: Treatment of Hepatic Metastases University of Frankfurt, Frankfurt, Germany
6/9/89	Surgical Grand Rounds: Treatment of Hepatic Metastases University Hospital of Lausanne Lausanne, Switzerland
6/11/89	Surgical Grand Rounds: Treatment of Hepatic Metastases National Tumor Institute, Milan, Italy
6/15/89	Trial of Liver Resection and Intrahepatic Chemotherapy Regional Cancer Therapy: State of the Art and Innovative Approaches. Memorial Sloan-Kettering Cancer Center, NY, NY
9/13/89	The Surgical and Medical Management of Liver Metastasis Oncology Grand Rounds New York University Medical Center, NY, NY
2/14/90	Experience With Splenectomies in Patients with AIDS or HIV Seropositivity. New York Surgical Society
8/16/90	Intraarterial Chemotherapy for the Treatment of Secondary Liver Tumors. 15th Internation Cancer Congress of the International Union for Cancer Control. Hamburg, Germany
1/25/91	Treatment of Hepatic Metastases by Surgery and Infusion. Combined Medical and Surgical Oncology Rounds University of Pittsburgh
2/13/91	Treatment of Hepatic Metastases from Colorectal Cancer with Intraarterial Therapy and Resection Roswell Park Memorial Institute, Buffalo, NY
2/27/91	Treatment of Hepatic Metastases from Colorectal Cancer with Intraarterial Therapy and Resection. Grand Rounds Sharp Memorial Hospital, San Diego, California

3/2/91	Treatment of Hepatic Metastases from Colorectal Cancer with Intraarterial Therapy and Resection Shiley Infusaid Meeting, Orlando, Florida
4/17/91	Surgical Resection of Hepatic Metastases from Colorectal Carcinoma. Evan and Marion Helfaer Distinguished Lecture, Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin
	Circadian Rhythm Influences The Toxicity of Continuous Hepatic Arterial Infusion of Recombinant IL-2. ASCO, Houston, Texas
6/19/91	Randomized Studies of Hepatic Arterial Infusion of FUDR in Patients with Liver Metastases from colon cancer. V. International Conference on Advances in Regional Cancer Treatment, Rosenheim, Germany
9/12/91	Treatment of Hepatic Metastases. Oncology Rounds, Rush Presbyterian Medical Center, Chicago, Illionois
9/24/91	Combined Modality Treatment for Resectable Metastatic Colorectal Carcinoma to the Liver: Surgical Resection of Hepatic Metastases in Combination with Continuous Infusion of Chemotherapy. GI Tumor Conference U. of Michigan, Ann Arbor,MI
10/4/91	Hepatic Resection: When, What Kind, and for Which Patients? 2nd International Workshop on Colorectal Cancer. Rome, Italy.
11/3/91	Intergroup Proctocol on Hepatic Metastases. The American Liver Surgery Group. Chicago Illinois
11/6/91	Breast Cancer in the Elderly. St. Vincent's Department of Geriatrics Grand Rounds. New York, N.Y.
12/12/91	Combined Modality Treatment for Resectable Metastatic Colorectal Carcinoma to the liver: Surgical Resection of Hepatic Metastases in combination with Continuous Infusion of Chemotherapy Grand Round Mt. Zion - UCSF Surgical Department, San Francisco, California.
1/09/92	Combined Modality Treatment for ResectableMetastatic Colorectal Carcinoma to the liver: Surgical Resection of Hepatic Metastases in combination with Continuous Infusion of Chemotherapy Methodist Hospital and CCOP, Minneapolis, Minn.
1/13/92	Modern Hematology/Oncology Course Lecture "Liver Resection and Use of the Infusaid Pump for Metastatic Colorectal Carcinoma to the Liver". Grand Rounds UCLA - Hematology/Oncology Department Los Angeles, California.

	Philadelphia and New York Surgical Societies. University Club, New York, N.Y.
4/14/93	Breast Cancer in the Elderly, Geriatric Medicine Conference, North Shore University Hospital-Cornell University Medical College, Manhasset, New York.
10/5/93	Management of Liver Metastasis, at Medical Grand Rounds, Raritan Bay Medical Center, Perth Amboy, New Jersey.
11/22/93	Surgical Rounds at Flinders Medical Center, Adelaide, Australia.
11/22/93	Lecture at Royal Adelaide Hospital, Adelaide, Australia.
11/26/93	Treatment of Liver Metastases, at 20th Annual Scientific Meeting of Clinical Oncological Society of Australia, Inc. (COSA), Perth, Australia.
11/26/93	State-of-the-Art in Cancer Therapy @ 20th Annual Scientific Meeting of COSA, Perth, Australia.
11/26/93	Adjuvant Treatment of G.I. Malignancy @ 20th Annual Scientific Meeting of COSA, Melbourne, Australia.
11/29/93	The Treatment of Colorectal Cancer, @ Anti-Cancer Council of Victoria, Perth, Australia.
12/2/93	Grand Rounds at Repatriation General Hospital, Concord, Australia.
4/4/94	Hepatic Metastases From Colorectal Cancer Past, Present and Future Therapies". The Clarence Schein Lecture Series Grand Rounds Lectureship at Montefiore Medical Center, New York City.
9/12/94	Circadian Patterning of Interleukin-2 Hepatic Artery Infusions as a Treatment for Hepatoma. GI Conference Memorial Sloan-Kettering Cancer Center, New York City.
9/20/94	Circadian Patterning of Interleukin-2 Hepatic Artery Infusions as a Treatment for Hepatoma. Medical Conference Hospital Paul Brousse, Villejuif, France.
9/27/94	Treatment of Colo-Rectal Liver Metastasis. Up to date in the Surgical Treatment of Pancreatic and Hepatobiliary Tumors - International Meeting, Universita Degli di Verona, Verona, Italy.

1997	Member of Site Visit Review Team of the American College of Surgeons Oncology Trials Group.
1996	Vice President of the Association of Women Surgeons and President Elect
1996	Faculty Member of ASCO/AACR Workshop entitled "Methods in Clincal Cancer Research"
1996	Member of the GI Program Commitee, ASCO
1996	U.S. Delegate to the Women's Health Forum.
1996	Member of NCI Review Committee of Emory University Comprehensive Cancer Center
1996	Member, ASCO Audit and Finance Committee
1996	Editorial Board, Cancer Management
1995 - 1993	Member of the Program Advisory Committee of the National Institutes of Health's Women's Health Initiative Program.
1995 - 1993	Executive Committee of the Program Advisory Committee of the National Institutes of Health's Women's Health Initiative Program.
1995	Chair, Immunology Devices Panel, Food and Drug Administration
1995	President of the New York Cancer Society
1994 - 1992	Member of the Legislative Affairs Committee of the Society of Surgical Oncology.
1994 - 1991	Member of Public Relations Committee, American Society of Clinical Oncology
1994	Member of NCI Review Committee of Yale University Comprehensive Cancer Center
1994	Member of Special Study Section for NCI Grants on Minimal Invasive Surgery
1993 - 1991	Member of the Clinical Trials Consultancy Group of the Society of Surgical Oncology
1993	Head of Development and Strategic Planning for Association of Women Surgeons.

1992	Editorial Board, Regional Cancer Treatment: International Journal of Oncology
1991 - 1986	Member of the Training Committee of the Society of Surgical Oncology
1991	Member of the Local Arrangement Committee Society of Surgical Oncology
1988	Editorial Board, HPB Surgery: A world Journal of Hepatic, Pancreatic and Billiary Surgery
1993 - 1994	President-Elect of the New York Cancer Society
1991 - 1993	Vice President of the New York Cancer Society
1989 - 1991	Treasurer of the New York Cancer Society
1988	Marshal - Harvard University Graduation
1972	American Medical Women's Association, Inc. Award for Scholastic Achievement
1969	Founder of the Organization of Female Medical Students College of Physicians and Surgeons
1968 - 1965	Member of the Study Group on Women's Education with Dr. Greta Bibring, Radcliffe College
1968	Class Marshal, Radcliffe College
1968	Cum Laude in Biology, Harvard University

INVESTIGATIONAL PROTOCOLS AND GRANTS

CURRENT:	Principal Investigator of the Intergroup protocol ECOG 1292, SWOG 9250, CALGB 9395: Phase II Intergroup prospectively randomiized trial of perioperative 5FU after curative resection followed by 5 FU/levamisole for patients with colon cancer.
	Co-PI of the ECOG Protocol 3292: Biologic correlates to response and survival in colon cancer.

Principal Investigator of the Intergroup protocol 9288, SWOG 8990: Combined modality treatment of hepatic metastases from colorectal cancer.

Principal Investigator of CALGB protocol 9670, Barriers to Participation of Older Women with Breast Cancer in Clinical Trials: A Pilot Study.

Co-PI CALGB protocol 9481: Phase III Study of Hepatic Artery FUDR, Leucovorin (LV) and Dexamethasone versus systemic 5-Fu and LV as treatment for hepatic metastases from colorectal cancer.

Co-Investigator of the Long Island Breast Cancer Study Project.

Co-investigator of the NIH study: Genetics of Breast Cancer Among Women of Jewish Ancestry.

Principal investigator of Schering- Plough Research Institute: Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using SCH 58500 (rAd/p53) Via Hepatic Artery Infusion: A Phase I Study.

Principal Investigator of Matrix Pharmaceuticals- #417-96-2: A Two-Stage Phase II Safety and Efficacy Study of IntraDose (Displatin/Epinephrine) Injectable Gel Administered to Patients with Unresectable Primary Hepatocellular Carcinoma.

Principal Investigator of Matrix Pharmaceuticals - #405-96-2: A Two-Stage Phase II Safety and Efficacy Study of Intradose (Cisplatin/Epinephrine) Injectable Gel Administered to Patients with Unresectable Intrahepatic Colorectal Metastases.

PAST PROJECTS:

Principal Investigator, Community Clinical Oncology Program (CCOP) of St. Vincent's Hospital, 1987 - 1990

Principal Investigator of St. Vincent's Hospital and Medical Center Protocol: Long Term Continuous Recombinant Interleukin-2 Infusion and Oral AZT as a Treatment for Acquired Immune Deficiency Syndrome. Funded for $25,000 by the Rudin Foundation Grant.

Cummings Foundation Grant $60,000 for expanded Breast Self Examination Teaching Program 1989 - 1992.

Infusaid Grant for $10,000 for research on Continuous Hepatic Artery Infusion in Rat Tumor Model 1989.

Medtronics Grant for $10,000 for research on Continuous Hepatic Artery Infusion in Rat Tumor Model 1989.

PI of North Shore University Hospital study: Phase I study of continuous infusion IL-2 given with a circadian modified pattern.

Co-investigator of the Cold Spring Harbor Project:Genetic analysis of human breast cancer.

Co-investigator of the Cold Spring Harbor Project:Telomerase activation in colon cancer.

Co-PI of the American Health Foundation grant: Environmental Factors and Breast Cancer in High Risk Areas.

Co-PI of North Shore University Hospital study: The use of Positron Emission Tomography (PET Scan) versus the Technesium 99-sestemibi scan for breast and axillary lymph node imaging.

Co- PI of North Shore University Hospital study: Sentinel Lymph Node Study: A study to determine the reliability of sentinel lymph nodes to detect cancer and determine the role of preoperative lymphoscintigraphy in women with tumors in the inner half of the breast through post procedure data collection.

Co-PI of North Shore University Hospital study: United States Surgical Corporation: Advanced Breast Biopsy System for Excisional Breast Biopsy.

Co-PI of NYU Gemzar Study at NSUH: Phase I/II study of induction chemotherapy with Gemcitabine (gemzar) and Cisplatin followed by combined chemo-radiation and/or surgical resection for locally advanced pancreatic cancer.

Co-PI of University of Michigan Study at North Shore University Hospital: Staging Breast Cancer with Positron Emission Tomography; A Multicenter Study sponsored by the NCI

PRESENTATIONS

1/16/82	Splenectomy for the Treatment of Hairy-Cell Leukemia Annual Meeting of the Southern California Chapter, American College of Surgeons
1/24/83	Experience with Combined Modality Treatment of Hepatic Metastases from Colorectal Primaries Annual Meeting of the Southern California Chapter, American College of Surgeons

5/24/84	The Detection of Liver Metastases by Laboratory Test International Symposium on Liver Metastasis, Boerhaave Committee for Postgraduate Medical Education, Faculty of Medicine. University of Leiden, The Netherlands
5/13-17/84	Combined Modality Treatment of Hepatic Metastases from Colorectal Cancer The Society of Surgical Oncology, Thirty-Seventh Annual Cancer Symposium, New York, NY
9/13-15/84	The Biology and Treatment of Colorectal Cancer Metastasis National Large Bowel Cancer Project. The University of Texas System Cancer Center - M.D. Anderson Hospital and Tumor Institute, Houston, Texas
11/15/84	Treatment for Metastatic Colorectal Cancer Foothill Presbyterian Hospital, Glendora, California
	Presentation of Laboratory Research City of Hope Hem-Oncology Conference
12/19/84	Treatment of Hepatic Metastases from Colorectal Cancer Cedars-Sinai Grand Rounds, Los Angeles, California
1/19/85	Management of Cancer of the Liver American College of Surgeons, Coronado, California
3/30/85	Treatment of Liver Metastases City of Hope Chapter, Las Vegas, Nevada
4/4/85	Surgical Treatment of Breast Cancer Grand Rounds, Long Beach Community Hospital, Long Beach, California
4/19/85	Infusaid Pump Treatment Versus Surgical Resection in Hepatic Metastases from Colon Cancer Grand Rounds, VA Wadsworth Medical Center, Los Angeles, California
5/6/85	Hepatic Infusaid Pump City of Hope Medical Oncology Research Group
5/9/85	Hepatic Artery Perfusion as an Adjuvant to Resection of Hepatic Metastases: Rationale and Results to Date Workshop for the Design and Implementation of Adjuvant Treatments Following Resection of Hepatic Metastases form Colorectal Cancer, Bethesda, Maryland
5/21/85	Complication with Continuous Hepatic Artery Chemotherapy Via and Implantable Pump American Society of Clinical Oncology, Houston, Texas
6/14/85	Hepatic Chemotherapy Pump Current Concepts in Radiation Oncology, City of Hope
8/26/85	Hepatic Resection and Regional Perfusion: A Randomized Protocol on Treatment of Hepatic Metastases Advances in Regional Cancer Therapy, Giessen, West Germany

2/13/86	Treatment of Colorectal Metastases to the Liver Northridge Hospital Medical Center
3/86	Adenocarcinoma in the Axillary Nodes with no known Primary Cancer Pacific Coast Surgical Association, Maui, Hawaii
3/7/86	Visiting Professor Tufts University, Boston, Massachusetts
6/9/86	Does Ultrasound Dissector (CUSA) Improve the Quality of Hepato-Pancreatic-Biliary Surgery? 1st World Congress on Hepato-Pancreatic Biliary Surgery, Lund, Sweden Resection of Liver Metastases - Where Do We Stand - Instructor 72nd Clinical Congress of the American College of Surgeons, New Orleans, Louisiana
10/4/86	Surgical Grand Rounds - Treatment of Colorectal Metastases to the Liver St. Joseph's Hospital, Paterson, New Jersey
11/12/86	Hepatic Resection and Hepatic Artery Infusion for Metastatic Colorectal Cancer Annual Cancer Seminar Update in Cancer Therapy - The American Cancer Society, New York Division
11/15/86	Surgical Grand Rounds - Treatment of Colorectal Metastases to the Liver Marshall University, West Virginia
6/5/87	Use of Ultrasonic Fragmentation in Abdominal Surgery Mount Sinai Hospital and New York City, The Page & William Black Post Graduate School of Medicine
3/9/88	Biological Response Modifiers and AIDS: A Nursing Prospective St. Vincent's Hospital and Medical Center
5/31/88	Surgical Treatment of Hepatic Metastases from Colorectal Primaries 2nd World Congress on Hepato-Pancreato Biliary Surgery, Amsterdam
10/5/88	Update on Treatment Modalities: Implications for Support in Decision Making American Cancer Society The Fifteenth Inga Thornblad Oncologic Conference Beth Israel Medical Center
3/5/89	Randomized Study of Intrahepatic vs Systemic Infusion of FUDR In Patients With Liver Metastases 2nd Biennial Conference on Chemotherapy of Infectious Diseases and Malignancies. Montreux, Switzerland
5/17/89	Treatment of Hepatic Metastases

1/23/92	Breast Cancer in the Elderly, The New York Academy of Medicine, Section on Geriatric Medicine:Symposium Cancer in Aging Women and Men, New York, N.Y.
2/12/92	"Improving Responses in Hepatomas with Circadian Patterned Infusion-A study of Continuous Hepatic Artery Infusion (CHAI) of Recombinant Interleukin-2 (rIL-2)" - New York Surgical Society
2/29/92	"Treatment of Liver Metastasis from Colorectal Cancer" Surgical Grand Rounds, Georgetown University Hospital, Washington DC
4/02/92	"Intra-Arterial Chemotherapy" - Department of Medicin Institute Gustave-Roussy, Villejuif, France
4/04/92	"Hepatic Resection and Intra Arterial Therapy" - Hospital Paul Broussy, Villejuif, France
4/05/92	"Circadian Rhythm Modulation of Intra Arterial IL-2 Therapy" Hospital Salpietre, Paris, France
6/07/92	"Reduction of the Toxicity of Continuous Hepatic Artery Infusion of Interleukin-2 with Circadian Patterning" 4th World Congress of Hepato-Pancreato-Billiary Surgery, Hong Kong
6/08/92	"The Effect on Liver Metastases of Circadian Patterning of Continuous Hepatic Artery Infusion (CHAI) of FUDR" 4th World Congress of Hepato-Pancreato-Billiary Surgery, Hong Kong
9/17/92	Liver Metastases, New York, Long Island College Hospital's '92 - '93 Grand Rounds Program
10/23/92	Breast Cancer - The Women in Science Section of the New York Academy of Sciences Symposium, " Forging a Women's Health Research Agenda: Policy Issues for the 1990's,
12/04/92	Randomized IA vs. Systemic vs. Resection of 1-3 Liver Metastases. Special International Columbus Meeting on Surgical Oncology, Genoa, Italy.
3/4/93	Adjuvant treatment of Colon Cancer, Medical Grand Rounds, Medical Center of Delaware, Christiana Hospital Wilmington, Delaware
3/4/93	Treatment of Metastatic Colon Cancer to the Liver, Combined Oncology Rounds, Medical Center of Delaware, Christiana Hospital, Wilmington, Delaware
3/10/93	Tumor Immunotherapy, Discussant at the Combined Boston,

10/10/94	Surgical Treatment of Hepatic Metastases. GI Surgery Course. American College of Surgeons Meeting, Chicago, Illinois.
1/12/95	Treatment of Hepatic Metastases. Surgical Grand Rounds Universtiy of Chicago, Chicago, Illinois.
5/20/95	Educational Symposia: Regional Therapies for Advanced
5/21/95	Colorectal Carcinoma, American Society of Clinical Oncology, Los Angeles, CA.
5/23/95	Discussant for Gastrointestinal Tract Slide Session, American Society for Clinical Oncology, Los Angeles, CA.
6/23/95	Hepatic Metastases. Congress of Clinical Oncology of Argentina, Buenos Aires.
6/24/95	Regional Chemotherapy to the Liver. Congress of Clinical Oncology of Argentina, Buenos Aires.
7/22/95	Moderator of the Panel: Controversies in the management of breast cancer. Assoc. of Women Surgeons. San Diego, CA.
11/13/95	Traveling Oncology Consultant Program sponsored by the American Cancer Society, Southern California.
2/26/96	"Hepatic Resection for Metastatic Carcinoma". Grand Rounds - St. Charles Hospital, Port Jefferson, New York
3/22/96	Poster Presentation: "Inhibition of Interleukin-2 (IL-2) Toxicity by CNI 1493". Society of Surgical Oncology Meeting - Atlanta,Georgia.
4/16/96	American College of Surgeons Spring Meeting -Moderator-Postgraduate Course - Commission on Cancer. New York, N.Y.
4/16/96	Treatment of Liver Metastases, ACS Spring Meeting, NYC
5/9/96	Speaker on "Cancer Clinic Day" for the Long Island chapter of the American College of Surgeons, "Treatment of Liver Metastases". Russo's on the Bay - Howard Beach, N.Y.
5/18/96	Adjuvant Treatment of Colon Cancer, Post graduate course, Digestive Diseases Week, San Francisco, CA.
5/22/96	Society for Surgery of the Alimentary Tract, Consensus Panel on Liver Metastases, San Francisco, CA
8/17/96	Workshop Faculty Clinical Trial Design for Regional Therapeutics, Joint AACR/ASCO on Methods in Clinical Cancer Research, Park City, Utah

11/28/96	Visiting Professor, Lecture on Liver Metastases, University of Navarra, Pamplona, Spain
11/30/96	Treatment of Recurrences from Colorectal Cancer, Symposium on treatment of cancer recurrence, Barcelona, Spain.
3/10/97	Hepatic Metastases from Colorectal Cancer, AIOM National Conference on Colorectal Cancer, Milan, Italy.
3/19/97	Breast Cancer Genetics. American Cancer Society Clinical Update. Sarah Lawrence University, Bronxville, New York.
3/25/97	Breast Cancer in the Elderly. Department of Obstetrics & Gynecology Grand Rounds. Albert Einstein Medical Center, New York.
11/21/97	Visiting Professor, Lecture on Metastatic Melanoma, University of Virginia, Charlottesville, Virginia.
4/9/98	Treatment of Hepatic metastases, Surgical Grand Rounds, Columbia University College of Physicians and Surgeons, New York.
4/22-24/98	Faculty leader of American College of Surgeons Course on Treatment of Cancer. Kluj Romania.
9/18/98	Regional infusion of hepatic metastases. International Digestive Diseases conference, Madrid, Spain.
9/19/98	Use of Intradose Cisplatin and Epinephrine gel for the treatment of hepatic metastases. Berlin, Germany.
10/24/98	Superior survival of young women with melanoma. Commission on Cancer Annual Meeting. Orlando, Florida.
10/28/98	Faculty member of postgraduate course on *Image Guided Breast Biopsy*. Orlando, Florida.

PUBLICATIONS

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ABSTRACTS

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24. Kemeny M, Alava G, Oliver J, Smith FB: The Effect on Liver Metastases of Circadian Patterning of Continuous Hepatic Artery Infusion (CHAI) of FUDR. 4th World Congress of Hepato-Pancreato-Billiary Surgery, Hong Kong, June, 1992.

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BOOKS AND CHAPTERS

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Item # 10

FACSIMILE TRANSMISSION RECORD

FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING
AND RADIOPHARMACEUTICAL DRUG PRODUCTS (HFD-160)
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

Number of Pages (including cover sheet): 2

Date: April 2, 1999

To: Joanna Fowler

From: Kaye Cho, Pharm.D.

Fax #: (516) 344-7902

Fax #: (301) 480-6036

Phone #: (516) 344-4365

Phone #: (301) 827-7510

Message:

Hi, Joanna.

I've decided to send you a memorandum instead of our Tcon minutes. I hope this will serve your need. Please let me know if you need anything else.

Thanks,
Kaye

NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.

INTEROFFICE MEMORANDUM

TO: JOANNA FOWLER, BROOKHAVEN NATIONAL LABORATORY

FROM: KAYE CHO, PHARM.D., REGULATORY PROJECT MANAGER

SUBJECT: IND 55,193/TOXICOLOGY STUDY

DATE: 04/02/99

This memo is to let the sponsor of IND 55,193/[18]Ro41-0960 know that they have adequately addressed FDA's concerns for their proposed toxicology study. The Agency's comments were addressed during a teleconference on January 13, 1999. The sponsor can pursue their toxicology study for this IND.

Item # 11

DEPARTMENT OF THE ARMY
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
524 PALACKY STREET
FORT DETRICK, MARYLAND 21702-5024

REPLY TO ATTENTION OF

January 12, 1999

Congressionally Directed Medical Research Programs - BCRP A

Dr. Yu Shin Ding, Ph.D.
Brookhaven National Laboratory
Department of Chemistry
Lewis Road
Building 555
Upton, NY US 11973-5000

RE: BC980045 - "PET Imaging of Estrogen Metabolism in Breast Cancer"

STATUS: RECOMMENDED FOR FUNDING

Dear Dr. Ding:

I am pleased to inform you, on behalf of the U.S. Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs' Breast Cancer Research Program (BCRP), that your research proposal has been recommended for funding. This decision was made based on a two-tiered review process incorporating scientific merit review as the first tier and programmatic review as the second tier. An information paper describing these two review processes is enclosed. A summary statement detailing the scientific review and critique of your submission is also enclosed.

Your proposal was recommended for funding from the highly competitive pool of submissions. We have made this decision based on your proposal's high scientific merit and relevance to the programmatic goals of the BCRP, with the belief that this project may add significantly to our understanding of breast cancer.

A contracting specialist from the U.S. Army Medical Research Acquisition Activity (USAMRAA) will contact your administrative representative authorized to negotiate contracts/grants. In addition, you may be contacted by our Regulatory Affairs Office if clarification of Human Use or Animal Use issues becomes necessary.

If you have not yet submitted your Human/Animal Use and Safety Appendices, please do so immediately.

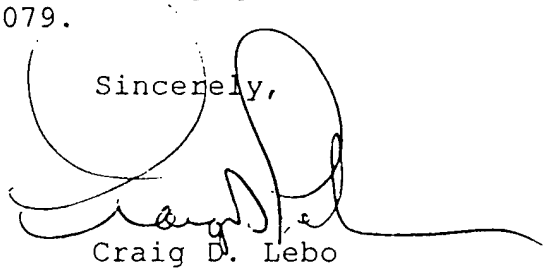
Specific requirements regarding appendices can be found in the Program Announcement for BCRP (March 31, 1998) on pages 27-28 and 45-47, as well as in Appendices 4-7 (pages A31-A65). Please submit five copies of the appropriate appendices before **January 26, 1999** to:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-PLF/Ms. Jennifer Secula
Building 524 (Breast Cancer Research Program)
Fort Detrick, MD 21702-5024

If you have already received funding elsewhere and no longer wish to be considered by the BCRP, please notify us by Fax (301) 619-7796 or by certified/overnight mail sent to the above address. Also, please note that any letter of withdrawal must be co-signed by an administrator from your Grants and Contracts Office.

We look forward to working with you and to the realization of the goals and objectives outlined in your proposal. Please direct any questions to the USAMRMC at (301) 619-7079.

Sincerely,



Craig D. Lebo
Deputy for Acquisition Division

Enclosures

Item # 12

11.0 Protocol Submission Checklist (Complete the following check with your proposal application.)

PROTOCOL TITLE: PET Imaging of Estrogen Metabolism in Breast Cancer
PRINCIPAL INVESTIGATOR'S NAME: YU-SHIN DING, Ph.D. PROPOSAL NO: BC 980045
INSTITUTION: Brookhaven National Laboratory

All Protocols:

✓ Consent Form(s)

NA If potential commercial use of sample(s) or future use of sample(s) in other studies, a Sample Donation consent form is required.

NA With HIV Testing, documentation of consent for HIV antibody testing, if scheduled, may be addressed in the body of the consent form or as separate HIV test consent form.

✓ Protocol

✓ Curriculum Vitae or Biosketch for Principal Investigator and Medical Monitor

✓ Scientific Review/Peer Review Approval(s)

✓ Letter from the IRB Chairperson with the following protocol information: (a) MPA number, (b) risk level that the IRB classified the protocol (c) date of IRB approval, and (d) next continuing review date

NA Copy of Recruitment Advertisement(s) and/or poster(s)

Investigational New Drug (IND) Protocols - additional requirements:

✓ Document specifying IND Number

NA Investigator's Brochure

✓ Copy of Case Report Forms (blank)

Medical Device Protocols – additional requirements:

NA Document from manufacturer declaring level of risk for device (non-significant risk or significant risk) & IDE form

N/A Document specifying IDE Number

N/A Manufacturer's device manual/ device information

Protocol Submission Checklist (cont.)

What type of study is proposed?

___	Phase I Clinical Trial	___	Survey/Medical Record Review	___	Community Intervention
___	Phase II Clinical Trial	___	Cohort (longitudinal study)	___	Laboratory Experiment
___	Phase III Clinical Trial	___	Retrospective (case-control)	___	Tissue Only
___	Multicenter Trial	___	Program/Policy Study	___	Qualitative Study
✓	Pilot Study	___	Cross-Sectional (prevalence)	___	Other: _____

Check all procedures applicable to this protocol:

✓	Experimental Drug/Medications IND# 66193	___	Prosthetic Orthopedic Devices
___	Marketed Agent, but Unapproved Use IND# _____	___	Nutrition/Metabolism Study
___	Experimental Device, IDE# _____	___	Tissue/Organ Transplant
___	Immunological Study	✓	Radiation or Radioactive Material
___	Artificial Organ Study	___	Human Embryos
___	Experimental Treatments	✓	Diagnostic Procedures
___	Experimental Surgery	___	Anatomical Substances Biological Specimens

Other: _____

Drug (s) to be used: _____ Drug Type* _____

*Drug Type may be chosen from the following list or other type may be stated as appropriate:

Analgesics	Anti-cancer drugs	Cardiac drugs	Hematologic agents
Anesthetics	Anti-convulsants	Diuretics	Hormones
Anti-allergy drugs	Anti-hypertensive drugs	Drugs affecting respiration	Tranquilizers/psychotropic dr
Anti-arrhythmic drugs	Anti-Parkinson agents	Eye/Optical drugs	Vitamins/Minerals
Antibiotics/anti-infective agent	Autonomic drugs	Gastrointestinal drugs	

Human Subject Information:

Age range of subjects: >18

# of subjects expected to be enrolled: Total # of subjects locally 20

If multicenter study, total # of subjects at all centers _____

Subject Gender: ___ Male ✓ Female ___ Both ___ Non-Consenting Subjects

Subject Age:	___ Infant	___ Child	___ Adolescent	✓ Adult ___ Ge
Vulnerable Subject Class:	___ Prisoners	___ Minorities	___ HIV +	___ Psychologically Impair
Subject Recruitment:	___ In-Patients	✓ Out-Patients	___ Students/Employees	___ Paid Volunteers

Principal Investigator's Signature

8/3/2000
Date

Appendix B

Brookhaven National Laboratory

Clinical Research Center

Upton, New York 11973

IRB PROTOCOL

IRB Title: PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960

Project (IRB) No.: 324

Principal Investigator: _____ Date: _____

Yu-Shin Ding

IRB 324 Protocol

Table of Contents

IRB Protocol: 324: PET Studies of Catechol-o-methyltransferase (COMT) with [18F]Ro41-0960

1. Study Rationale

A and B. Background and Preliminary Data:

It is well known that many breast tumors are associated with estrogen and there is evidence that the presence of catecholestrogens in breast tumors cause changes in the DNA which may lead to uncontrolled cell growth. Catecholestrogens are broken down by an enzyme called catechol-O-methyltransferase (COMT). COMT is known to be elevated in malignant breast tumors, and abnormal COMT genetics have recently been found in individuals with breast cancer. We have developed [^{18}F]labeled Ro41-0960, the first radiotracer for visualizing COMT with positron emission tomography (PET). The hypothesis that [^{18}F]Ro41-0960 can map COMT *in* vivo was demonstrated in baboon and mouse (Ding, et al., 1996; Ding, et al., 1997). The tracer uptake is highest in liver and kidney, which is consistent with high levels of COMT in these peripheral organs. Dose response curves and time course studies with PET for unlabeled Ro41-0960 in baboon indicated that the binding of [^{18}F]Ro41-0960 to COMT sites in periphery is saturable and sensitive to COMT inhibition (Ding, et al., 1998). A complementary *ex vivo* approach in which we correlated the radiotracer uptake with COMT activities in rodents further demonstrated the ability of [^{18}F]Ro41-0960 in mapping COMT activity *in vivo*. Recently, we have adapted our COMT enzyme assay method and performed studies in breast tumor tissue samples from cancer patients undergoing surgery (Ding, et al., 1999). COMT activities in normal and abnormal human breast tissues from the same patient were compared. Though COMT activities varied among subjects, preliminary results showed elevated COMT activities in the breast tumor tissues of all patients studied; the difference can be as high as 26 fold increase. This can be a potential signal to noise ratio for the PET studies in breast cancer that we have proposed.

Ding Y.-S., Gatley S. J., Fowler J. S., Chen R., Volkow N. D., Logan J., Shea C. E., Sugano Y., Koomen J. (1996) Mapping Catechol-*O*-methyltrans-ferase in vivo: Initial Studies with [^{18}F]Ro41-0960. *Life Sciences* **58**, 195-208.

Ding Y.-S., Sugano Y., Koomen J., Fowler J. S., Aggarwal D., Ferrieri R., Schlyer D. (1997) Synthesis of [^{18}F]RO41-0960, A Potent Catechol-O-Methyltransferase Inhibitor, for PET Studies. *J. Label. Cmpd. Radiopharm.* **39**, 303-318.

Ding Y.-S., Logan J.S., Gatley S.J., Fowler J.S., Volkow N.D. (1998) PET Studies of Peripheral Catechol-O-methyltransferase in Non-human Primates Using [^{18}F]Ro41-0960. *J. Neural. Transm.*, 105, 1199-1211.

Ding Y.-S. , Pyatt B. , Fowler J.S. , Volkow N.D. , Abumrad N., DeRisi.D. (1999) A Potential Use of [^{18}F]Ro41-0960, a Selective COMT Inhibitor, for PET Imaging of Estrogen Metabolism in Breast Cancer. *J. Nucl. Med.* **40**, 100P.

2. Design of the Trial

A. Introduction: Our studies have demonstrated that the activity of COMT, a soluble enzyme that catalyzes the O-methylation of various catechols including catecholestrogens, was significantly elevated in highly malignant human breast tumor tissue. The feasibility of mapping COMT *in vivo* with PET is supported by our recent baboon studies using [^{18}F]Ro41-0960. This proposed application involves the use of [^{18}F]Ro41-0960 and PET to localize and quantitate COMT in the human body as a marker for breast tumors.

The study will be carried out in breast cancer patients recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Patients slated to

undergo surgery will be scanned within four weeks of surgery and samples of tumor and normal tissue will be retained for histopathological characterization and for assay of COMT activity. Each subject will have one PET scan with [^{18}F]Ro41-0960. These studies will set the stage in developing a diagnostic tool to characterize the biochemical profile of breast tumors in human subjects. If successful, the benefit of this new method would lead to a better understanding of the role of COMT in the metastases of human breast cancer, as well as reducing the need for unnecessary breast biopsies and enhancing the staging capabilities of current diagnostic procedures. These studies may also provide information that suggests new treatments for breast cancer.

B. Hypothesis: Because COMT activity is significantly elevated in highly malignant human breast tumors and the uptake of [^{18}F]Ro41-0960 correlates very well with the activity of COMT in baboon and mouse, we hypothesize that an elevated uptake of [^{18}F]Ro41-0960 can be visualized with PET in breast cancer patients and that the elevated uptake will correlate with the elevated COMT activity in breast tumor.

C. Study Aims

i. Objectives: To test whether an elevated uptake of [^{18}F]Ro41-0960 can be visualized with PET in breast cancer patients.

ii. Specific aims and hypothesis:

a. To use PET to measure the uptake of [^{18}F]Ro41-0960 in breast cancer patients.

b. To compare the radiotracer uptake in the tumor breast with that in the normal breast from the same patient.

c. To compare COMT activity in the tumor breast tissue with that in the normal breast tissue from the same patient.

d. Hypothesis: see C2B

D. Eligibility criteria

i. Inclusion criteria:

1. positive needle biopsy, palpable breast tumor
2. Ability to understand and give informed consent
3. >18 years of age

ii. Exclusion Criteria:

1. pregnant
2. uncontrolled medical disease including

   diabetes, hepatic or renal disorders,

   Parkinson's or endocrine disease,

   psychiatric illness requiring antipsychotic drugs

3. prior history of radiation and/or chemotherapy
4. history of anaphylactic reactions
5. medications which may interfere with COMT activity

   (for example, tolcapone or other COMT inhibitors)
6. individuals with known sensitivity to the use of local anesthetics

E. Outcome Measures:

i. Primary:

1. A [^{18}F]Ro41-0960/PET scan
2. COMT activities in tumor breast tissue and normal breast tissue.

ii. Secondary: not applicable

iii. Descriptive measures: cardiac monitoring (all subjects).

F. Sample size and analysis plan: Breast cancer patients (n=20) will be recruited from Stony Brook who will be scheduled for their surgery within four weeks of their PET scan. For the analysis, we will compare the radiotracer uptake in the tumor breast with that in the normal breast from the same patient to determine if they are different. We will also compare COMT activity in the tumor breast tissue with that in the normal breast tissue from the same patient.

Power calculation: tumor characteristics are expected to vary and we can only estimate and not predict, the numbers to enter into a power calculation, nor do we know the normal variability. However, we will assume a 10% intersubject variability and a 20% difference in uptake between tumor and normal tissue. We need a sample size of 9 to achieve a significane of $p<0.05$. We want to recruit 20 patients because of anticipated difficulties in follow-through for patients who have just been diagnosed with breast cancer.

G. Recruitment;

i. Introduction: Breast cancer patients will be recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook.

ii. Resources: Pat Hentschel at Stony Brook serves as our recruiter. Naomi Pappas at BNL serves as our coordinator.

iii. Recruitment Plan: Breast cancer patients appearing to be eligible are then invited to BNL for prescreening and [^{18}F]Ro41-0960 /PET scan.

iv. Recruitment timeline: The rate limiting step is the identification and recruitment of breast cancer patients who meet inclusion criteria. We anticipate that the study will be completed in three years.

H. Randomization: not applicable

I. Masking: not applicable

J. Study flow sheet (see attached table).

K. Subject study flow sheet (see attached table)

L. Risks and benefits from participation in the study

RISKS: **Catheter Placement for Injection and Blood Sampling:** Arterial catheterization has the following rare but possible complications: pain during placement of the catheter, a risk of bleeding at the skin puncture site, the possibility of local infection, temporary or permanent impairment of the blood supply to portions of your hand. Pain during the placement of the catheter is minimized by the use of a local anesthetic, which will be injected at the site of skin puncture. The chance of excessive bleeding from the catheter site will be minimized by a prolonged application of pressure. The risk of infection will be minimized by the use of local antiseptic measures prior to catheter placement. The use of an arterial catheter also involves some additional risk of temporary interference with arterial blood flow to the hand involved. Such complications are uncommon and can be controlled by the physician supervising the study. In addition, the placement is done by a trained physician and we exclude any subjects with peripheral artery disease and/or in whom there is not a palpable ulnar artery. Whenever blood is removed or a substance is injected by needle into a vein, there is minor discomfort and a slight possibility of local bleeding in the tissues, bruising and fainting. The injection of the anesthetic, xylocaine, may be painful.

You should refrain from moderate to heavy exercise for a few days following this procedure, especially using the hand where the catheterization was performed.

Adverse allergic reactions: Because the radioactivity of F-18 decays very rapidly (the time required to decay half amount of the radioactivity is 110 minutes), the radiotracer cannot be tested for sterility and freedom from fever producing compounds before it is administered. However, the system for production is checked frequently and consistently produces a sterile product, free from fever producing compounds. No such allergic reactions have been encountered. In addition, all of the radiotracers are administered in very small chemical doses (less than 50 micrograms per radiotracer injection). This dose is below that which will cause a pharmacological effect.

Radiation Exposure: The total amount of radiation exposure you will receive from this study (1 injection) is 445 mrem (effective dose equivalent). For comparison the average radiation background in the U.S. is about 360 mrem/year. Radiation doses from standard clinical procedures are: Bone scan- 440 mrem; Thallium stress test – 4400 mrem and X-ray – 10 mrem. A potential side effect of radiation is the induction of cancer. However, no harm in a human individual or in a large population exposed at doses as low as that delivered in this procedure has been observed. Thus the estimation of the risk of harm can be obtained only by extrapolation from much higher doses. The calculated risk is small and would raise the "normal" risk of lethal cancer, which is about 20% to 20.01%.

If you are a woman of childbearing potential you should practice effective birth control while participating in this study. If you should become pregnant, you must inform your doctor immediately. Exposure to radiation is harmful to a fetus.

BENEFITS: There may be no direct benefit to you, however, information gained from this study may help development of a better understanding and diagnosis of breast cancer.

3. Subject visits and treatment

A. Introduction

Breast cancer patients: this study takes one day. Each subject (breast cancer patient) has one PET scan with [^{18}F]Ro41-0960. Subjects are recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Subjects who have scheduled for their surgery will have initial screening and physical exams at Stony Brook to determine that the subjects meet inclusion/exclusion criteria prior to receiving the PET scan at BNL.

B. Screening visit: The screening visit at BNL will comprise a pregnancy test and brief physical exams to determine that the subject meets inclusion/exclusion criteria. Screening visit will take place the day of the PET scan.

C. Following visits: not applicable.

D. Study termination and close out: When the data is analyzed and a research manuscript is written and accepted for publication, then the study is terminated by filling out a termination form and submitting to the IRB.

E. Assessment timetable: necessary assessments are made on the day specified in the study flow.

F. Subject follow-up: A follow-up call is made the next working day by BNL after the study is completed to see if the subject has any study-related questions or problems. This is recorded in the medical record.

4. Description of examination procedures:

A. Rationale for selected eligibility criteria: Inclusion criteria are**:** a positive needle biopsy, palpable breast tumor, and no prior history of radiation and/or chemotherapy. Pregnant patients will be excluded from the study based on a pregnancy test (urine) on the day of the PET study. Subjects with any evidence of uncontrolled medical disease including diabetes, hepatic or renal disorders, Parkinson's or endocrine disease, psychiatric illness requiring antipsychotic drugs, or a history of anaphylactic reaction will be excluded. This eligibility criteria was chosen to minimize variables which may confound the interpretation of the study.

B. Cognitive assessment: during the physical examination, the physician will test the subject's orientation, cognition and judgment as to their ability to understand and give informed consent.

C. Descriptive measures: cardiac monitoring (all subjects).

D. Self-report measures: not applicable.

5. Data management

A. Data handling and collection: (see attachment including location of data)

B. Subject Accrual: In order to obtain an accurate count of new subjects enrolled for each study for reporting to the IRB, we will use multiple cross-checks following these steps. This applies to all PET protocols. We will obtain the subject accrual for each CIRC proposal by obtaining a printout of the new subjects from the present PET database capturing only new

subjects for the period requested by the IRB. We will check number and the PET run numbers against the records of N. Pappas (recruiter) and G-J Wang (physician) and reconcile this if there are differences.

C. Study documents (kept in Case Report Form)

PET Subject Information
Drug History (Doctor)
PET Run Data Sheet(s)
Study Flow Sheet
Inclusion/Exclusion Criteria
Cardiac Monitoring

D. Data entry: Physical examinations are administered by doctors or nurses and entered by hand. Information specific to the PET scan protocol is entered by the PET operator. The location of these records is described above in 5A attachment. Data in protocol specific forms is managed by Christopher Wong (ext 4989).

6. Study operations and quality assurance

A. Quality assurance: Details of procedures and documentation for critical measurements and materials are highlighted below.

During the course of the trial a Clinical Research Monitor will review the study progress, compliance to protocol and accuracy of the Case Report Forms in accordance with established BNL medical research monitoring procedures.

A Principal Investigator must receive approval from the IRB any time s/he plans to deviate from the protocol originally approved by the IRB via an Addendum Review. Such a change may be requested by a Principal Investigator for any reason including an unanticipated reaction of a subject to a research procedure. No change in protocols can be initiated until the IRB has approved the change.

PET cameras: PET cameras are checked daily for stability of gantry electronics, photomultiplier tubes, and crystals using solid Ge-68 sources. This procedure is automated for the HR47+ and runs every morning before arrival of the subject. Results indicating the status of the gantry are printed automatically and report individual detector and total gantry deviations from values acquired during the last camera calibration and normalization. Acceptable ranges are reported along with the daily QC measure. A similar procedure and analysis is carried out manually on the CTI 931 camera. In this case only the total deviation of all detectors is in the gantry is reported. Acceptable ranges for QC measures are also indicated on the computer output. For both cameras a visual inspection of the QC sinogram is made before study protocols are continued.

After stability testing, radioactivity from a low activity (< 1 microCurie) Ge-68 "aliquot" source is acquired. Both singles (HR+ only) and coincidence counts are recorded in both 2D and 3D (HR+ only) acquisition modes.

All results from daily QC tests are recorded in both the camera log book and the Building 906 Quality Assurance Log Book. PET cameras are calibrated and normalized according to standard procedures for Building 906 as dictated by daily QC test results or under special circumstances including detector replacement, software upgrade, etc. Calibrations and normalizations are

carried out using uniform Ge-68 phantoms that have been previously calibrated using 18F-flouride.

Picker Well Counter: Well counter stability is determined daily using a sealed calibrated radioactivity source (Ge-68 and/or Cs-137). Source counts are recorded daily on run sheets and in the PET Clinical Laboratory Quality Assurance Log. Absolute counter efficiency is determined bi-annually according to standard procedures using 18F-fluoride and liquid scintillation counting. Results are recorded in a calibration notebook stored in the Building 901 Radiotracer Laboratory supervisor's office.

Capintec Dose Calibrator: The Capintec dose calibrator is calibrated every 6 months according to standard procedures using mCi levels of 18F and/or 11C radioactivity. Previous and new calibrator setpoints for measuring 18F and 11C are recorded in a calibration log book located in the Radiotracer Laboratory supervisor's office.

Radiotracers: All radiotracer quality assurance and batch production records are stored in notebooks in the GMP lab in Building 901. Sterility and pyrogenicity records for each delivery of radiotracer are kept in Room 383; Building 555 (Chemistry). Radiotracers undergo a battery of appropriate quality assurance tests. All results must lie within established acceptable ranges. Acceptance of radiotracer is verified by a designated chemist's signature in the batch records.

B. Subject information and informed consent: The subject fills out a Subject Information Form containing demographic information. The subject also fills out a medical History form which is reviewed by the physician. The physician meets with the subject and explains the procedures in the study. The subject is asked to sign the consent forms after the procedures have been explained. Signed consent forms are kept in the Medical Record.

C. Drug dosage and supply: C-11 and F-18 labeled radiotracers are prepared each time they are needed because of the short half life of carbon-11 (20.4 minutes) and F-18 (110 minutes). Quality control records for each batch are kept in lab 113 of bldg 901 and in lab 383 of bldg 555 as described in 6A. Once the radiotracer ([^{18}F]Ro41-0960) is delivered to the PET Imaging Laboratory, a dose of 5 millicuries of the radiotracer (approximately equal to 445 mrem of radiation) with less than 50 micrograms of chemical mass is withdrawn into a syringe and counted in a dose calibrator and the time is recorded on the PET run data sheet. It is then injected and the time of injection is recorded. The empty syringe is counted again and the time recorded to obtain an accurate measure of the dose which the patient received. The physician also logs the dose and time that it is injected in the Medical Record on the form "Clinical Report of PET Study" and in the Internal Radioisotope Summary Sheet in the subject's medical record.

D. Monitoring for medication compliance and adverse effects.

Definition: Adverse Event

An adverse event temporally related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbations of preexisting conditions. Include the following in all IND safety reports: Subject identification number and initials; associate investigator's name and name of MTF; subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route and duration of treatment, and date of last dose.

Cardiac monitoring is carried out during the study. Close monitoring of the subject during the study and the follow-up call will pick up adverse events if they occur.

Reporting of Serious and Unexpected Adverse Events

Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Medical monitor

John L. Coulehan, MD, MPH, FACP, is a medical monitor for this study.

E. Unscheduled termination/removal of subject: If a subject withdraws early from the study or if the physician determined that he/she does not meet eligibility criteria after enrollment in the study (for example, if a subject has a positive urine pregnancy test during the screening visit for the PET study), then the subject is withdrawn and the reason noted in the chart.

7. References (see 1A above)

2 J. Study Flow Sheet

1. Subject (a breast cancer patient) is recruited by Dr. Margaret Kemeny of the Department of Surgery, State University of New York at Stony Brook. Subject who has scheduled for her surgery will have initial screening and physical exams at Stony Brook to determine that she meets inclusion/exclusion criteria prior to the day she receives the PET scan. The subject is scanned before surgery.
2. Subject arrives at CRC (Clinical Research Center) / PET for initial BNL screening.
3. Subject signs consent 647 and fills out the Subject Identification Form.
4. Subject receives laboratory tests.
5. Subject receives a brief history/physical examination to assess ability to understand and give consent and to determine if he/she meets inclusion criteria.
6. If inclusion criteria are met, the study consent (#710) is administered. At this point the subject is enrolled.
7. The hand is warmed. The arterial and venous catheters are inserted.
8. Subject is positioned in the PET and has a transmission scan performed.
9. Cardiac monitoring is performed during the study.
10. The radiotracer ([^{18}F]Ro41-0960) is injected and scanning commences for 64 minutes. Blood samples are taken and analyzed during this time for 18F activity and plasma analysis.
11. The arterial and venous catheters are removed
12. At the end of the scanning period the subject is asked to urinate.
13. The subject is given a meal.
14. The subject is paid and given a comment form.
15. The subject receives a follow-up 12 lead EKG at CRC after the study and then discharged.
16. The subject receives a follow-up call on the next working day.

REMINDER: DETAILS OF ALL ADVERSE EVENTS MUST BE SOLICITED AND RECORDED AT EACH VISIT.

2K. Subject Study Flow Sheet

Procedure	Prescreen Visit (Stony Brook)**	Visit (BNL)	Surgery Visit (Stony Brook)
informed consent (SUNY)	x		
informed consent (#647)		x	
informed consent (#710)		x	
EKG	x	x (after PET scan)	
blood lab	x		
review-inclusion/exclusion	x	x	
medical history	x		
complete physical exam	x		
pregnancy test	x	x	
brief physical exam		x	
drug history	x	x	
PET subject information		x	
PET scan		x	
tissue samples			x***
volunteer fee paid		x	
Follow-up call		x*	

* next working day

** records are maintained at Stony Brook. A copy is sent to BNL and maintained in the medical record.

*** tissue samples are obtained at surgery, frozen and transferred to BNL for analysis at a later date.

5A. Data Handling and Collection

Summary of data types and location for all Human PET experiments

Radioactivity Measurements

PET Image Data

1. Ecat 931 Tomograph

Electronic records (image files) are stored in an optical disk library located in Room 3 and Room 8 in Building 906. Hard copy records of recent run sheets are stored in the Room 3 in Building 906. Older run sheets are archived in Room 9. All raw and reconstructed data are also stored on 8mm tape in Room 9.

2. Siemens Hr47+ Tomograph

Electronic records (volume files) are stored on hard disks mounted to a Sun Ultra60 workstation named ultrabrain3d.pet.bnl.gov in Room 8 in Building 906. Hard copy records (run sheets) are stored in Room 3 and Room 9 in Building 906. All raw and reconstructed data are also stored on 4mm tape in Room 9.

Plasma concentration

Electronic records (cnt and vol files) are stored on a hard disk mounted to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records of plasma data are stored in Room 3 (recent) and Room 9 (archived).

Metabolite correction

Electronic records (met files) are stored on a hard disk connected to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records are stored outside room 134-I in Building 901W in metal filing cabinets.

Urine

Urine toxicology screen is kept in the Medical Record. Urine radioactivity measurements, if obtained, are recorded on the PET blood lab data sheet.

Injected Dose

Electron records (lab files) are stored on a hard disk mounted to the Sun Ultra60 workstation named ultrahr47.pet.bnl.gov in Room 3 in Building 906. Hard copy records (PET blood lab data sheets) are stored in Room 3 (recent) and Room 9 (archived).

A. Region of Interest (ROI) data

1. Ecat 931 Tomograph

Electronic records (ROI files) are stored on a hard disk mounted to the Sun workstation named viewbrain.pet.bnl.gov in Room 8 in Building 906.

2. Siemens Hr47+ Tomograph

Electronic records (ROI files) are stored on a hard disk mounted to a Sun Ultra60 workstation named ultrabrain3d.pet.bnl.gov in Room 8 in Building 906.

B. Blood and Urine analysis

Hard copy records of blood or urine measurements are stored in locked file cabinets in Rooms 5-33 and 5-31 in Building 490.

I. Cardiovascular Data

Hardcopy records are stored in locked file cabinets in Rooms 5-33 and 5-31 in Building 490.

II. Plasma analysis

Hardcopy records are stored in locked file cabinets in Room 5-33 and 5-31 in Building 490.

Electronic source file machine:directory key:

Source file location is identified by the workstation's official Internet Protocol name (IP name) followed by the exact Unix filesystem separated by a colon (**machine.name:filesystem**)

1. 931 Image files (.img*)** - viewbrain.pet.bnl.gov:/data1 (when optical is mounted)

2. HR47+ Volume files (.v*)** – ultrabrain3d.pet.bnl.gov:/home/data3 or /home/data4

Data is normally accessed through CTI's Ecat v. 7.2 software and database using the workstations ultrabrain3d.pet.bnl.gov and u2brain.pet.bnl.gov

3. Plasma radioactivity files *(*.cnt and*.vol)*:

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. rcs)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0 or /usr2/data0/xxx where xxx is the study code (e.g. ccs).

4. Dose, plasma glucose, and scanning information (.lab files*):**

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. mrh)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0

or /usr2/data0/xxx where xxx is the study code (e.g. ras)

5. Metabolite correction files (.met*):**

ultrahr47.pet.bnl.gov:/home/data1/export/data0

or /home/data1/export/data0/xxx where "xxx" is the study code (e.g. nas)

Data may also be accessed through the path sun.pet.bnl.gov:/usr2/data0

or /usr2/data0/xxx where xxx is the study code (e.g. omh). Metabolite files are also stored on the PC named hotlab.pet.bnl.gov in Building 901.

6. ROI files *(*.roi and *.txt)*:

931 (.roi*)** – viewbrain.pet.bnl.gov:/petsys/xxx or /petd/xxx or /petd1/xxx where "xxx" is the investigator ID code (e.g. jsf) or other investigator defined project code.

HR47+ (.txt*)** - ultrabrain3d.pet.bnl.gov:/hrpd/xxx where "xxx" is the investigator ID code (e.g. sld)

Subject Initials:_____

Witness Initials:_____

Consent Form (SUNY, Stony Brook)

TITLE: Pre-Op PET Studies of Catechol -O- Methyltransferase (COMT) with (^{18}F) Ro41-0960 for Patients with Breast Cancer

PRINCIPAL INVESTIGATOR: Margaret Kemeny, M.D., Nora Volkow, M.D., Yu-Shin Ding, PhD

You are being asked to participate in a research study.

PURPOSE: The purpose of this study is to determine whether a certain enzyme, COMT, which is elevated in certain breast tumors, can be seen in the breast with PET, a medical imaging method. If so, this information may be of value in breast cancer diagnosis and treatment. There will be twenty patients enrolled in this research study. .

The procedure will involve PET scanning with a radioactive tracer called [^{18}F] Ro41-0960, which attaches to COMT. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which was removed from your breast. If PET and [^{18}F] Ro41-0960 provides diagnostic information, it could reduce the need for unnecessary breast biopsies and enhance the staging capabilities of current diagnostic procedures. This study may also provide knowledge, which may suggest new treatments for breast cancer.

PROCEDURES: If you decide to be in this study you will have a PET scan, blood work and an evaluation, at Brookhaven National Laboratory, within 4 weeks before your surgery.

Preparation for the PET scan: As part of the evaluation procedure at Brookhaven National Laboratory, you will undergo a physical examination which will include a medical history. This will also include lab testing of blood (approximately 2 tablespoons) and urine chemistry and a urine test for pregnancy (if you are a female subject of childbearing age). The investigators may also ask for your alcohol and drug history. In some subjects, an electrocardiogram (EKG) may also be performed to ensure that there are no problems with the functioning of the heart. You will be asked to refrain from taking any other drugs while you are participating in this study unless you receive permission from your physician.

Subject Initials:_____

Witness Initials:_____

PET Scans: Before and during scanning you will wear a heart monitor to record your heart rate and blood pressure. Before the injection of the radiotracers, the breast area will

be scanned two or three times, for about 5 minutes each while it is surrounded by a radioactive substance. You will be expected to lie still during the PET scanning.

This study will involve the administration of radioactive [^{18}F] Ro41-0960. The scan will require about 64 minutes. You will be asked to urinate at the end of the scanning to reduce the radiation exposure to your lower abdominal region. There is a possibility that you may be rescanned 1 hour later for 10-20 minutes.

Arterial and Venous Catheterization: It is necessary to place a catheter in a vein in your arm for the radiotracer injection. It is also necessary to obtain either arterialized venous or arterial blood samples, for some of the measurements needed in this work. To obtain these blood samples, you will either have a catheter placed in a vein in your hand (for arterialized venous samples) or a catheter placed in a radial artery in the wrist area (for arterial samples). For arterialized venous samples, your hand will be warmed after the catheter is in place to promote the mixing of arterial venous blood, a condition which is needed for the blood sampling, which will occur during the PET scan. If blood samples are to be taken from an artery, the physician will perform a painless test to determine whether the arteries that supply blood to the hand are functioning. Only if the test is normal will the investigators proceed with the study. The placing of the arterial catheters is generally more painful and uncomfortable than is the case with intravenous catheters. A dose of xylocaine will be given under the skin by a small needle before the catheterization to relieve pain. During these procedures, the catheter may be in place for up to 7 hours.

Throughout the procedure, the investigators will be obtaining blood samples to measure concentration of radiotracer in blood. A total of no more than 60 cc (4 tablespoons) of blood will be removed for any single injection of the radiotracer. Blood samples may also be analyzed for other measures, which the investigators need for the studies.

Your participation is expected to be about 6-8 hours for each day of participation. We may ask you to repeat this study in the future if your breast cancer recurs.

RISKS:

Investigational New Drugs: The investigational agent to be used in this study is not approved by the Food and Drug Administration (FDA) for commercial use; however, FDA has permitted its use in this research study.

Catheter Placement for Injection and Blood Sampling: Arterial catheterization has the following rare but possible complications: pain during placement of the catheter, a risk of

Subject Initials:_____

Witness Initials:_____

bleeding at the skin puncture site, the possibility of local infection, temporary or permanent impairment of the blood supply to portions of your hand. Pain during the placement of the catheter is minimized by the use of a local anesthetic, which will be injected at the site of skin puncture. The chance of excessive bleeding from the catheter site will be minimized by a prolonged application of pressure. The risk of infection will be minimized by the use of local antiseptic measures prior to catheter placement. The use of an arterial catheter also involves some additional risk of temporary interference with arterial blood flow to the hand involved. Such complications are uncommon and can be controlled by the physician supervising the study. In addition, the placement is done by a trained physician and we exclude any subjects with peripheral artery disease and/or in whom there is not a palpable ulnar artery. Whenever blood is removed or a substance is injected by needle into a vein, there is minor discomfort and a slight possibility of local bleeding in the tissues, bruising and fainting. The injection of the anesthetic, xylocaine, may be painful. However, You will be excluded from this study if you have known sensitivity to the use of local anesthetics.

You should refrain from moderate to heavy exercise for a few days following this procedure, especially using the hand where the catheterization was performed.

Adverse allergic reactions: Because of the short half-life of F-18 (110 minutes), the radiotracer cannot be tested for sterility and freedom from fever producing compounds before it is administered. However, the system for production is checked frequently and consistently produces a sterile product, free from fever producing compounds. No such allergic reactions have been encountered. In addition, all of the radiotracers are administered in very small chemical doses (less than 50 micrograms per radiotracer injection). This dose is below that which will cause a pharmacological effect.

Radiation Exposure: The total amount of radiation exposure you will receive from this study (1 injection) is 445 mrem (effective dose equivalent). For comparison the average radiation background in the U.S. is about 360 mrem/year. Radiation doses from standard clinical procedures are: Bone scan- 440 mrem; Thallium stress test – 4400 mrem; X-ray –10 mrem. A potential side effect of radiation is the induction of cancer. However, no harm in a human individual or in a large population exposed at doses as low as that delivered in this procedure has been observed. Thus the estimation of the risk of harm can be obtained only by extrapolation from much higher doses. The calculated risk is small and would raise the "normal" risk of lethal cancer, which is about 20% to 20.01%.

Cardiovascular reactions: No cardiovascular reactions have been ever observed in our pre-clinical studies in non-human primates. There might be slight reduction in blood pressure and heart rate if a large amount of the drug is administered. However, the administration a dose of 5 millicuries of the radiotracer with less than 50 micrograms of chemical mass, which is 10,000 x below the doses of the drug that are reported to have

Subject Initials:_____

Witness Initials:_____

been administered in animals without untoward effects, should not cause clinically detectable pharmacological effects.

Pregnancy Prevention

If you are a woman of childbearing potential you should practice effective birth control while participating in this study. If you should become pregnant, you must inform your doctor immediately. Exposure to radiation is harmful to a fetus.
You should also avoid becoming pregnant for at least 3 days after participation in the study. To avoid becoming pregnant, you should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing are not totally effective in preventing pregnancy.

BENEFITS: There may be no direct benefit to you, however, information gained from this study may help development of a better understanding and diagnosis of breast cancer. Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research.

PAYMENT TO YOU: You will receive $ 100.00 for the day of participation in this study at Brookhaven National Laboratory as well as any traveling expenses.

COSTS TO YOU: There will be no charge to you or your insurance company for any treatment or care that you receive as part of this study.

CONFIDENTIALITY: The following procedures will be followed in an effort to keep your personal information confidential in this study. Your identity will be coded, and all data will be kept in a secured, limited access location. Your identity will not be revealed in any publication or presentation of the results of this research. However, confidentiality cannot be guaranteed; your personal information may be disclosed if required by law.

To ensure that this research activity is being conducted properly, SUNY Stony Brook's Committee on Research Involving Human Subjects, the Food and Drug Administration, Brookhaven National Laboratory, The National Institute of Health, A representative of the funding institution, U.S. Army Medical Research and Materiel Command, may have the right to review study and medical records, but confidentiality will be maintained as allowed by law.

Volunteer Registry Data Base Requirements

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this

Subject Initials:_____

Witness Initials:_____

confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

IN CASE OF INJURY:

Medical Care for Research Related Injury

Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

If you are injured as a result of being on this study, you should contact Dr. Margaret Kemeny at 631-444-1793. The services of SUNY – Stony Brook's University Hospital and Medical Center will be open to you in case of such injury. However, you or your insurance company will be responsible for payment of any resulting treatment and/or hospitalization.

****

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.
- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a copy of this consent form to keep.
- You do not waive any of your legal rights by signing this consent form.

Questions about the Study or Your Rights as a Research Subject

- If you have any questions about the study, you may contact Dr Margaret Kemeny at 631-444-1793.
- If you have any questions about your rights as a research subject, you may contact Dr. Robert Schneider, Committee on Research Involving Human Subjects,631-632-9036.

If you sign below, it means that you have read (or have read to you) the information given in this consent form, and you would like to be a volunteer in this study.

_____ _____

Subject Name Subject Address

_____

Subject Signature Date

Subject Initials:_____

Witness Initials:_____

_____

Printed Name and Signature of Person Obtaining Consent Date

I willingly agree that a piece of my tissue obtained from my surgery will be used for the research purposes of this study involving PET scanning.

_____

Subject name

_____

Subject Signature Date

_____

Printed Name and Signature of Person Obtaining Consent Date

Consent Form Number: 710
IRB Protocol Number: 324
Date of First Approval: 11/02/99
Date of Most Recent Approval 10/03/00
Date of Expiration: 10/03/01

Subject Number: _____
Subject Initials: _____
Witness Initials: _____

CLINICAL RESEARCH CENTER
MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973-5000
INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Title of Project: PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960
Funding: Department of Defense, Department of Energy

1. **You are invited to participate in a research project. The overall purpose of the research is**: to determine whether larger amounts of an enzyme (COMT) can be seen in breast cancer. There will be twenty patients enrolled in this research study.

2. **Your participation will involve the following:**

This study will use a brain imaging method called positron emission tomography (PET). A PET camera will take pictures of a radioactive molecule (radiotracer) that can be sent through the body's circulatory system. The radiotracer links itself with the COMT already in the tumor. If you have breast cancer and are scheduled to undergo surgery, you will have a PET scan within two weeks before the surgery. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which is removed during the surgery.

- The PET procedure: This is described in the PET Brochure that you have been given and the video that you have viewed.
- Preparation for the PET scan: Before scanning you will be fitted with a custom-made head holder that will hold your head steady while you are being scanned. You will then have a "transmission scan", a 15 minute scan to check your positioning in the PET scanner. Red lines will be drawn on your head with a washable marker to line up the PET scanner.
- Catheter placement and blood sampling: You will have two catheters (small plastic tubes) inserted, one in an artery in your the wrist for taking blood samples during the study and one in a vein in your arm for injecting the radiotracer and saline. A local anesthetic will be injected into your wrist before inserting the catheter in the artery, which may be in place for up to ten hours on each day of participation. During each scan about 4 tablespoons of blood will be taken, for a total of 8 tablespoons each day. The blood will be analyzed for radiotracer. This information will allow the investigators to form an accurate picture of the way your body functions.

3. **Your participation is expected to have the following duration:**

Six to eight hours for each day of participation. If there is a technical difficulty, the study could take up to 11 hours. You are only scheduled for one day at this time, but if the results from the preliminary studies are promising or your breast cancer returns, you may be asked to return for a second scan.

4. **There are certain risks and discomforts that may be associated with this research:**

Investigational New Drugs: The investigational agent to be used in this study is not approved by the Food and Drug Administration (FDA) for commercial use; however, FDA has permitted its use in this research study.

Subject Initials: _____
Witness Initials: _____

Consent form # 710

Catheter Placement for Injection and Blood Sampling: The PET study requires having a catheter (a plastic tube) inserted into a vein in your arm for radiotracer injection. Another catheter will be placed in an artery in your wrist for drawing blood samples. The use of this catheter has the following possible complications:

- Pain: There is a risk of pain during placement of the catheter. This will be minimized by the injection of a local anesthetic. However, You will be excluded from this study if you have known sensitivity to the use of local anesthetics.
- Bleeding: There is a risk of bleeding at the skin puncture site. The risk will be minimized by applying pressure directly to the puncture site. You should refrain from moderate to heavy exercise of the hand where the catheter was placed for at least three days after the study.
- Local infection: There is a possibility of local infection. This will be reduced by using antiseptic and by using sterilized catheters.
- Impairment of the blood supply to portions of your hand: There is a very small possibility of temporary or permanent impairment of blood supply to your hand. To avoid this, the physician will perform a painless test to determine whether the arteries that supply blood to the hand are functioning. If it appears that blood is not flowing to your hand through the artery, the catheter will be placed in your vein.

1. Risks of heparin administration: None, unless the person has a clotting disease, which would exclude them from this study.

Adverse reactions: No allergic reactions caused by contamination of the radiotracer have been encountered. In addition, all of the radiotracers are administered in very small chemical doses so that you will not notice any behavioral or physical change when it is injected.

Radiation Exposure: The radiation dose from this procedure is 445 mrem. For comparison, the average background radiation in the United States is 360 mrem per year. Example radiation doses from standard clinical procedures are: Bone scan – 440 mrem; thallium stress test - 4400 mrem; X-ray – 10 mrem.

Cardiovascular reactions: No cardiovascular reactions have been ever observed in our pre-clinical studies in non-human primates. There might be slight reduction in blood pressure and heart rate if a large amount of the drug is administered. However, the administration a dose of 5 millicuries of the radiotracer with less than 50 micrograms of chemical mass, which is 10,000 x below the doses of the drug that are reported to have been administered in animals without untoward effects, should not cause clinically detectable pharmacological effects.

5. **The following alternatives are available for obtaining the same knowledge as will result from this study:** There are no alternative procedures which can be expected to give the same information as is expected from this study.

6. **The possible benefits to you/and or to society from this research are:** As a research subject, you are asked to participate in procedures and studies which are not established medical practice. These studies are undertaken to learn more about the human body in health and disease; to discover and evaluate new methods of

Subject Initials: _____

Witness Initials: _____

Consent form # 710

diagnosis and treatment of certain diseases; to examine the effectiveness of current methods of treatment in hope that a better understanding will lead to more effective control.

There is no direct benefit to you; however, information gained from this study may help development of a better understanding and diagnosis of breast cancer.

7. **Brookhaven National Laboratory will take all reasonable measures to protect the confidentiality of your records and your identity will not be revealed in any publication resulting from this study.** This includes information disclosed by you in completing any research project questionnaire or information obtained from you during participation in this research project. There is a possibility that your medical record, including identifying information, may be inspected by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. A representative of the funding institution, U.S. Army Medical Research and Materiel Command, may also inspect these records.

Volunteer Registry Data Base Requirements

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

8. **Your participation is totally voluntary** and you are free to withdraw from the study at any time and to discontinue participation without prejudice. The investigator may withdraw you from this research study if at any time circumstances arise which warrant doing so. You will be given a copy of the Participants Bill of rights.

9. **If you receive a physical injury resulting from the research procedures,** medical treatment will be provided free of charge; however, monetary compensation is not available.

10. **If it is discovered that you have some unrelated medical illness** during your participation in this project, you will be informed and advised to seek appropriate medical care. BNL will not compensate you for any underlying condition discovered during the study.

11. **Other institutions may be collaborating with Brookhaven** and therefore you may be contacted by the following institutions in order to arrange for appointments: None.

12. **You will receive a volunteer fee:** You will receive $100.00 for each day of participation in this study.

13. If you have any questions or concerns regarding this study, or if any problems arise, you should call the Responsible or the Participating Physician. You may also direct questions about your rights as a research

Brookhaven National Laboratory

Clinical Research Center

IRB 324

Subject Initials: _____

Witness Initials: _____

Consent form # 710

subject to the Clinical Research Center (CRC) Physician.
Responsible Physician: Nora D. Volkow Phone: 631 344-3335
Participating Physician: Gene-Jack Wang Phone: 631 344-3608
CRC Physician: Jack Coulehan Phone: 631 344-3672

You have read this consent form and have been given the opportunity to ask questions. You understand that you will also be given a copy for your records. You hereby consent to participate in this procedure.
PARTICIPANTS NAME: _____
PARTICIPANTS ADDRESS: _____
SIGNED BY: _____
(Subject and, when necessary, legal guardian) (Date)
The undersigned herewith affirms that they have explained the above and are willing to answer further inquiries.
WITNESS: _____ _____ _____
PRINTED NAME SIGNATURE (Date)

This consent form is valid for 2 months from the signature date

Consent Form Number: 647
IRB Protocol Number: All PET Protocols
Date of First Approval: 08/06/97
Date of Most Recent Approval: 05/02/00
Date of Expiration: 08/04/00

Subject Initials: _____
Witness Initials: _____

CLINICAL RESEARCH CENTER
MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973-5000

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Title of Project: LABORATORY TESTING FOR PET RESEARCH STUDY

1. **You are invited to participate in a research project.** The purpose of this series of tests given prior to your PET scans is to determine your eligibility to participate in the PET scans. The following tests with a check next to them will be performed.

2. **Your participation will involve the following:**

_____**Urine Test:** A urine test will be performed to measure the possible presence of drugs such as marijuana or cocaine. This test is performed to ensure that you have not taken drugs prior to the PET procedure, since this would interfere with the results obtained. This test will be repeated if you return on another day. You will be asked to give a small sample of urine some time after your arrival in a container provided for the specimen. Tests on the urine sample will be as requested by your physician.

__x__ **Pregnancy Test:** A small sample of your urine will be collected at the Clinical Laboratory to determine if you are pregnant. You will be asked to give a sample some time after your arrival in a container provided for the specimen. This test may be repeated each day of the PET scanning.

__x___**Electrocardiogram (EKG):** A ten lead EKG will be performed to determine if there are problems with the functioning of your heart. The leads are attached to an EKG machine which will record and analyze the electrical impulses of your heart.

_____ **Blood Chemistry:** To determine whether your blood cell counts and chemistry are within the normal ranges, approximately 25 ml (6 teaspoons) of blood will be withdrawn by venipuncture.

_____**Exercise:** To determine if you are able to participate in a study which requires you to run on a treadmill for 30 minutes, you will be asked to run on a treadmill for 30 minutes. The speed of the treadmill will be progressively increased for the first 15 minutes until you reach a sub maximal effort level. You will then run at this sub maximal level for another 15 minutes, but the pace will be slowed progressively for the last 5 minutes.

_____**Breath Test for Carbon Monoxide**: To determine the levels of carboxyhemoglobin in your blood as a measure of exposure (either active or passive) to cigarette smoke, you will be asked to take a deep breath in and to hold this for as long as possible and then to breathe out slowly and steadily through the mouthpiece of the Vitalograph measuring device over a period of 20 seconds.

_____**Tobacco Questionnaire:** You will be asked eight questions about your smoking habits to assess your degree of dependence on tobacco smoking.

Subject Initials: _____

Witness Initials: _____

Consent form # 647

_____**Brief Mental Assessment:** You will be asked several questions to evaluate your ability to understand the procedures.

__x__**Sensitivity to Local Anesthetics Questionnaire:** You will be excluded from this study if you have known sensitivity to the use of local ansthetics.

3. **Your participation is expected to have the following duration:**

Approximately 30 minutes total if all tests except the exercise are performed. The exercise portion is expected to take approximately 40 additional minutes.

4. **There are certain risks and discomforts that may be associated with this research:**

Blood Withdrawal: The blood withdrawal is of minimal risk; however, it can lead to certain discomfort. Also, in some instances, there may be small bruises where the needle was inserted and a few drops of blood may leak out after the needle is removed.

Exercise: As with regular exercise, the investigators expect that your heart rate and blood pressure will go up. However, the investigators have calculated the effort to be one which should be adjusted to your own responses and one to which you are used to. However, to minimize the possibility of any untoward reactions, your vital signs will be monitored throughout the procedure and a physician will remain by your side. The exercise will be terminated if the physician observes abnormal cardiac rhythm and/or if you feel dizzy or light headed.

Pregnancy Prevention

If you are a woman of childbearing potential you should practice effective birth control while participating in this study. If you should become pregnant, you must inform your doctor immediately. Exposure to radiation is harmful to a fetus.

You should also avoid becoming pregnant for at least 3 days after participation in the study. To avoid becoming pregnant, you should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing are not totally effective in preventing pregnancy.

5. **The following alternatives are available for obtaining the same knowledge as will result from this study:** None.

6. **The possible benefits to you/and or to society from this research are:**

As a research subject of the Clinical Research Center, Brookhaven National Laboratory, you are asked to participate in procedures and studies which are not established medical practice. These studies are undertaken to learn more about the human body in health and disease; to discover and evaluate new methods of diagnosis and treatment of certain diseases; to examine the effectiveness of current methods of treatment in hope that a better understanding will lead to more effective control or even its eradication.

There may be a benefit to you from the knowledge gained from the results of these tests.

Subject Initials: _____

Witness Initials: _____

Consent form # 647

7. **Brookhaven National Laboratory will take all reasonable measures to protect the confidentiality of your records and your identity will not be revealed in any publication resulting from this study.** This includes information disclosed by you in completing any research project questionnaire or information obtained from you during participation in this research project. There is a possibility that your medical record, including identifying information, may be inspected by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. A representative of the funding institution of this study, U.S. Army Medical Research and Materiel Command, may also inspect these records.

8. **Your participation is totally voluntary** and you are free to withdraw from the study at any time and to discontinue participation without prejudice. Results from these tests may disqualify you from acceptance as a volunteer for a PET protocol. You will be given a copy of the Participants Bill of Rights.

9. **If you receive a physical injury resulting from the research procedures,** medical treatment will be provided free of charge; however, monetary compensation is not available.

10. **If it is discovered that you have some unrelated medical illness** during your participation in this project, you will be informed and advised to seek appropriate medical care. BNL will not compensate you for any underlying condition discovered during the study.

11. **Other institutions may be collaborating with Brookhaven** and therefore you may be contacted by the following institutions in order to arrange for appointments: None.

12. **You will receive a volunteer fee:** You will receive $50 if you undergo all the laboratory tests and $25 if you only undergo urine testing. If you claimed to be drug-free and you urine tests are positive for drugs, you will not receive a volunteer fee for the Laboratory Testing. If you are selected to participate in the PET study today, you will receive an additional $50 ($100 total) for the day. You will be informed of the results of these tests. If you withhold any information during the telephone screening about any medications you may be taking (even therapeutic medications which you are using to treat illnesses that you may have), you will not receive the volunteer fee for the Laboratory testing. If this is discovered after you have been enrolled as a subject for a PET study, you will not receive a volunteer fee for the PET study.

13. If you have any questions or concerns regarding this study, or if any problems arise, you should call the Responsible or the Participating Physician. You may also direct questions about my rights as a research subject to the Clinical Research Center (CRC) Physician.

Responsible Physician: Nora D. Volkow Phone: 631 344-3335

Participating Physician: Gene-Jack Wang Phone: 631 344-3608

CRC Physician: Jack Coulehan Phone: 631 344-3672

You have read this consent form and have been given the opportunity to ask questions. You understand that you will also be given a copy for my records. You hereby consent to participate in this procedure.

PARTICIPANTS NAME: _____

Brookhaven National Laboratory

Clinical Research Center

IRB 324

Subject Initials: _____

Witness Initials: _____

Consent form # 647

PARTICIPANTS ADDRESS: _____

SIGNED BY: _____

(Subject and, when necessary, legal guardian) (Date)

The undersigned herewith affirms that they have explained the above and are willing to answer further inquiries.

WITNESS: _____ _____ _____

PRINTED NAME SIGNATURE (Date)

This consent form is valid for 2 months from the signature date

Appendix C

BROOKHAVEN NATIONAL LABORATORY
M E M O R A N D U M

DATE: April 17, 2001

TO: Y.S. Ding

FROM: M.C. Bogosian, Chair, Institutional Review Board (IRB) MCB/4

SUBJECT: **IRB Protocol 324** "PET Studies of Catechol-O-Methyltransferase (COMT) with [^{18}F]Ro-41-0960"

At the 04/17/01 IRB meeting, the annual recertification and reactivation of the above IRB protocol was approved.

Approval by the CRC Manager is required before work may begin under this protocol.

This protocol is approved until 03/27/02. This approval is given only for the protocol submitted; any changes must be approved by the IRB prior to being implemented.

You should be aware that all research outlined in this protocol must be carried out under approved Experimental Safety Review(s) (ESR) and that this application must contain the same information as that listed in the approved ESR(s). You must be aware that it is your responsibility to ensure that all individuals working on this protocol have been listed on an appropriate ESR and that their training is up to date.

Investigators must report any unanticipated problems promptly to the IRB.

IRB

M.C. Bogosian
B.D. Breitenstein
S. Mendelsohn
H.L. Atkins
D.J. Schlyer
R. Ferrieri
C. Schaefer
E.T. Lessard
J. Van't Hof
T. Butcher
J. Lombardo
J. Gisondo
E. Lowenstein
D. Dunn
E. Sokol
E. Weiss
K. Waterman
O. Gould

MCB:dm
IRB Form 010: Approved 08/04/98; Revised 06/01/99

INSTITUTIONAL REVIEW BOARD APPROVAL
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973

TITLE OF APPLICATION: PET Studies of Catechol-O-Methyltransferase (COMT) with [^{18}F]Ro-41-0960

PRINCIPAL INVESTIGATOR: Y.S. Ding

PROPOSAL SUMMARY: (Include total number of subjects to be studied each year and number who will undergo repeat studies, including frequency. **Must be in layperson's terms.**)

COMT (catechol-O-methyltransferase) is a natural enzyme in the body that is sometimes found in greater amounts in certain breast tumors. The purpose of this study is to determine whether the larger amounts of COMT can be seen in breast cancer with Positron Emission Tomography (PET), a medical imaging method similar to a camera, and whether this information can be of value in breast cancer diagnosis and treatment. The procedure will involve PET scanning with a tracer called [^{18}F]Ro-41-0960, which links itself with the COMT already in the tumor. Subjects with breast cancer who are scheduled to undergo surgery will have a PET scan within four to eight weeks preceding the surgery. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which is removed during the surgery. If PET and the experimental tracer [^{18}F]Ro-41-0960 provide diagnosis information, it could reduce the need for unnecessary biopsies and make current diagnostic procedure better. This study may also provide knowledge which may suggest new treatments for breast cancer. Twenty breast cancer patients will be studied.

This institution has an approved Federalwide Assurance on file with HHS which covers this activity.

FWA00000149 FWA Number

The above titled application has been reviewed and approved by the IRB in accordance with the Human Studies Rules and Regulations. All applicable approvals and consent forms from participating institutions are on file in the Office of Human Subjects Research Administration.

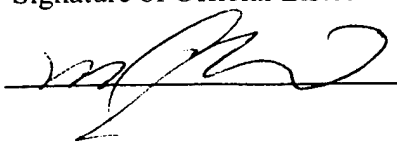
03/27/01 Date of IRB review and approval.
Applicable Consent Forms: # 647, 710
IND # (If applicable): 55,193

The official signing below certifies that the information provided on this form is correct and that the institution assumes responsibility for assuring required future reviews, approvals and submissions of certification.

Name, Address and Telephone No.
M.C. Bogosian
Bldg. 475D
Brookhaven National Laboratory
Upton, NY 11973
(631) 344-7338

Name and Title of Official
M.C. Bogosian
Chairman, Institutional Review Board

Signature of Official Listed



Consent Form Number: 324A
IRB Protocol Number: 324
Date of First Approval: 11/02/99
Date of Most Recent Approval 10/03/00
Date of Expiration: 10/03/01

Subject Initials:
Witness Initials:

CLINICAL RESEARCH CENTER
MEDICAL DEPARTMENT
BROOKHAVEN NATIONAL LABORATORY
UPTON, NY 11973-5000
INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Title of Project: PET Studies of Catechol-O-methyltransferase (COMT) with [^{18}F]Ro41-0960
Funding: Department of Defense, Department of Energy

1. **You are invited to participate in a research project. The overall purpose of the research is**: to determine whether larger amounts of an enzyme (COMT) can be seen in breast cancer in women. There will be twenty patients enrolled in this research study.

2. **Your participation will involve the following:**
This study will use an imaging method called positron emission tomography (PET). A PET camera will take pictures of a radioactive molecule (radiotracer) that can be sent through the body's circulatory system. The radiotracer links itself with the COMT already in the tumor. If you have breast cancer and are scheduled to undergo surgery, you will have a PET scan within four to eight weeks before the surgery. The results of the PET scan will be compared with the results obtained by examination of the surgical sample, which is removed during the surgery.

- The PET procedure: This is described in the PET Brochure that you have been given and the video that you have viewed.
- Preparation for the PET scan: Before scanning you will be positioned on the bed of the PET scanner so that your chest area is in the field of view. A special positioning bed will be used to minimize movement of your chest area during the scan. You will then have a "transmission scan", a 15 minute scan to check your positioning in the PET scanner.
- Catheter placement, Radiotracer Injection and blood sampling: You will have two catheters (small plastic tubes) inserted, one in an artery in your the wrist for taking blood samples during the study and one in a vein in your arm for injecting the radiotracer and saline. A local anesthetic (lidocaine) will be injected into your wrist before inserting the catheter in the artery. The radiotracer, [^{18}F]Ro-41-0960, will be injected into the vein in your arm and PET scanning of the chest area and possibly the abdomen will begin. During each scan about 4 tablespoons of blood will be taken, for a total of 8 tablespoons each day. The blood will be analyzed for radiotracer. This information will allow the investigators to form an accurate picture of the way your body functions. You will have saline/heparin solution (salt water containing heparin to prevent clotting) flowing through each catheter during the entire study.
- EKG: Two 12 lead EKG will be used prior to and at the end of the study, and a three-lead EKG will be used to continuously monitor your heart function throughout the entire study.

3. **Your participation is expected to have the following duration:**
Six to eight hours for each day of participation. If there is a technical difficulty, the study could take up to 11 hours. You are only scheduled for one day at this time, but if there is a technical problem, you may be asked to return for a second scan.

Subject Initials: _____

Witness Initials: _____

Consent form # 710

4. **There are certain risks and discomforts that may be associated with this research:**

Investigational New Drug: The investigational agent ([18F]Ro41-0960) to be used in this study has not been given to humans and is not approved by the Food and Drug Administration (FDA) for commercial use; however, the FDA has permitted its use in this research study.

Catheter Placement for Injection and Blood Sampling: The use of this catheter has the following possible complications:

- Pain: There is a risk of pain during placement of the catheter. This will be minimized by the injection of a local anesthetic. However, You will be excluded from this study if you have known sensitivity to the use of local anesthetics.
- Bleeding: There is a risk of bleeding at the skin puncture site. The risk will be minimized by applying pressure directly to the puncture site. You should refrain from moderate to heavy exercise of the hand where the catheter was placed for at least three days after the study.
- Local infection: There is a possibility of local infection. This will be reduced by using antiseptic and by using sterilized catheters.
- Impairment of the blood supply to portions of your hand: There is a very small possibility of temporary or permanent impairment of blood supply to your hand. To avoid this, the physician will perform a painless test to determine whether the arteries that supply blood to the hand are functioning. If it appears that blood is not flowing to your hand through the artery, the catheter will be placed in your vein.
- Risks of heparin administration: None, unless the person has a clotting disease, which would exclude them from this study.

Adverse reactions: No allergic reactions caused by contamination of the radiotracer have been encountered. In addition, all of the radiotracers are administered in very small chemical doses so we do not expect that you will notice any behavioral or physical change when it is injected.

Radiation Exposure: The radiation dose from this procedure is 445 mrem. For comparison, the average background radiation in the United States is 360 mrem per year. Example radiation doses from standard clinical procedures are: Bone scan – 440 mrem; thallium stress test - 4400 mrem; **X-ray – 10 mrem.**

Cardiovascular reactions: This drug has not been given to humans yet, but there were no cardiovascular effects observed in the animal studies. There might be slight reduction in blood pressure and heart rate if a large amount of the drug is administered. However, the administration a dose of 2-5 millicuries of the radiotracer with less than 50 micrograms of chemical mass, is 10,000 times below the doses of the drug that are reported to have been administered in animals without untoward effects, should not cause clinically detectable pharmacological effects, and we do not expect that you will notice any behavioral or physical change when it is injected.

5. **The following alternatives are available for obtaining the same knowledge as will result from this study:** There are no alternative procedures, which can be expected to give the same information as is expected from this study.

6. **The possible benefits to you/and or to society from this research are:** As a research subject, you are asked to participate in procedures and studies, which are not established medical practice. These studies are undertaken to learn more about the human body in health and disease; to discover and evaluate new methods of

diagnosis and treatment of certain diseases; to examine the effectiveness of current methods of treatment in hope that a better understanding will lead to more effective control.

There is no direct benefit to you; however, information gained from this study may help the development of a better understanding and diagnosis of breast cancer.

7. **Brookhaven National Laboratory will take all reasonable measures to protect the confidentiality of your records and your identity will not be revealed in any publication resulting from this study.** This includes information disclosed by you in completing any research project questionnaire or information obtained from you during participation in this research project. There is a possibility that your medical record, including identifying information, may be inspected by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. A representative of the funding institution, **U.S. Army Medical Research and Materiel Command,** may also inspect these records.

Volunteer Registry Data Base Requirements

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential database includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

8. **Your participation is totally voluntary** and you are free to withdraw from the study at any time and to discontinue participation without prejudice. The investigator may withdraw you from this research study if at any time circumstances arise which warrant doing so. You will be given a copy of the Participants Bill of rights.

9. **If you receive a physical injury resulting from the research procedures,** medical treatment will be provided free of charge; however, monetary compensation is not available.

10. **If it is discovered that you have some unrelated medical illness** during your participation in this project, you will be informed and advised to seek appropriate medical care. BNL will not compensate you for any underlying condition discovered during the study.

11. **Other institutions may be collaborating with Brookhaven** and therefore you may be contacted by the following institutions in order to arrange for appointments: State University of New York at Stony Brook.

12. **You will receive a volunteer fee:** You will receive $100.00 for each day of participation in this study.

13. If you have any questions or concerns regarding this study, or if any problems arise, you should call the Responsible or the Participating Physician. You may also direct questions about your rights as a research subject to the Clinical Research Center (CRC) Physician.

Responsible Physician: Nora D. Volkow Phone: 631 344-3335
Participating Physician: Gene-Jack Wang Phone: 631 344-3608

Brookhaven National Laboratory

Clinical Research Center

IRB 324

Subject Initials: _____

Witness Initials: _____

Consent form # 710

CRC Physician: Jack Coulehan Phone: 631 344-3672

You have read this consent form and have been given the opportunity to ask questions. You understand that you will also be given a copy for your records. You hereby consent to participate in this procedure.
PARTICIPANTS NAME:
PARTICIPANTS ADDRESS:

SIGNED BY: _____
(Subject and, when necessary, legal guardian) (Date)
The undersigned herewith affirms that they have explained the above and are willing to answer further inquiries.

WITNESS:_____
PRINTED NAME SIGNATURE (Date)

This consent form is valid for 2 months from the signature date